

Painweek.

ADVANCED EDUCATION

CERTIFICATION SERIES

CANNABINOIDS

A repeating pattern of cannabis leaves in a dark green color, serving as a background for the 'CANNABINOIDS' text.

Medical & Recreational Marijuana

Mark Garofoli, PharmD, MBA, BCGP, CPE

Faculty Disclosure

- **Consulting Fee:** HealthXL, Speranza
- **Other:** Expert Witness—Cardinal Health

This presentation was not a part of the presenter's official duties at the WVU and does not represent the opinion of WVU

Learning Objectives

- Identify the four main pharmacological properties of substances that are conducive to substance abuse.
- Distinguish the most common THC product formulations including combustibles, edibles, resin, and extracts based on pharmacological properties.
- Recall the pharmacological properties of various illegal synthetic cannabinoids with particular attention to the structural similarities to NSAID medications.

Substances of Abuse: Controlled Substance Classes

CONTROLLED SUBSTANCE CLASS	SUBSTANCES
C-I	Heroin, LSD, Marijuana, MDMA, & PCP
C-II	Cocaine, Fentanyl, & Methamphetamine
C-III	Ketamine
C-IV	Benzodiazepines
C-V	Promethazine with Codeine

Bad Drugs (Good Medicines?)

- Stimulants (cocaine, amphetamines, etc)
- Hallucinogens
- Cannabis/cannabinoids
- Opioids
- General sedatives (GABA-related, etc)
- Alcohol
- Nicotine/tobacco
- Inhalants
- COMBINATIONS (polypharmacy or “PolyStreet”)

It's All About the Dosage, Baby!

LETHAL DOSES OF COMMON CHEMICALS

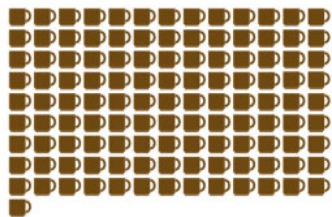
LD₅₀

LD₅₀ stands for 'median lethal dose', and is defined as the amount of a substance required to kill 50% of a test population of animals, expressed in mg per kg of body weight. Human LD₅₀ values are calculated from these tests. For ethical reasons, tests on animals to determine LD₅₀ are being phased out in favour of other methods.

The figures provided below are median lethal doses, and are rough averages for a body weight of 75kg, when the amount specified is taken all at once. Actual figures will vary depending on physical and medical condition.



WATER
6 LITRES



CAFFEINE
118 COFFEES
1 coffee - approx 240ml
(Or 175 shots of espresso)



ALCOHOL
13 SHOTS
Where 1 shot = 45 ml
(40% ABV)

© COMPOUND INTEREST 2014 - WWW.COMPOUNDCHEM.COM
Twitter: @compoundchem | Facebook: www.facebook.com/compoundchem
References & further information: www.compoundchem.com/2014/07/27/lethal-doses



APPLE SEEDS



CONTAIN AMYGDALIN
~0.6g/kg of seeds

PEARS



CONTAIN FORMALDEHYDE
~0.06g/kg

POTATOES



CONTAIN SOLANIN
~0.2g/kg
(higher in green potatoes)

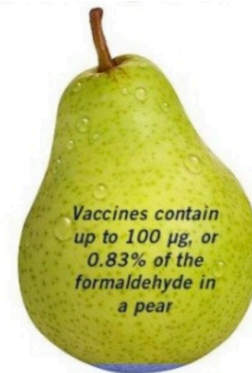
COURGETTES



CONTAIN CUCURBITACIN E
Variable
(higher in bitter courgettes)



A 200 g pear contains up to 12,000 µg of formaldehyde, naturally



Vaccines contain up to 100 µg, or 0.83% of the formaldehyde in a pear

The amount of formaldehyde in a vaccine is so tiny that it doesn't even affect the naturally occurring levels of formaldehyde in a child's blood.

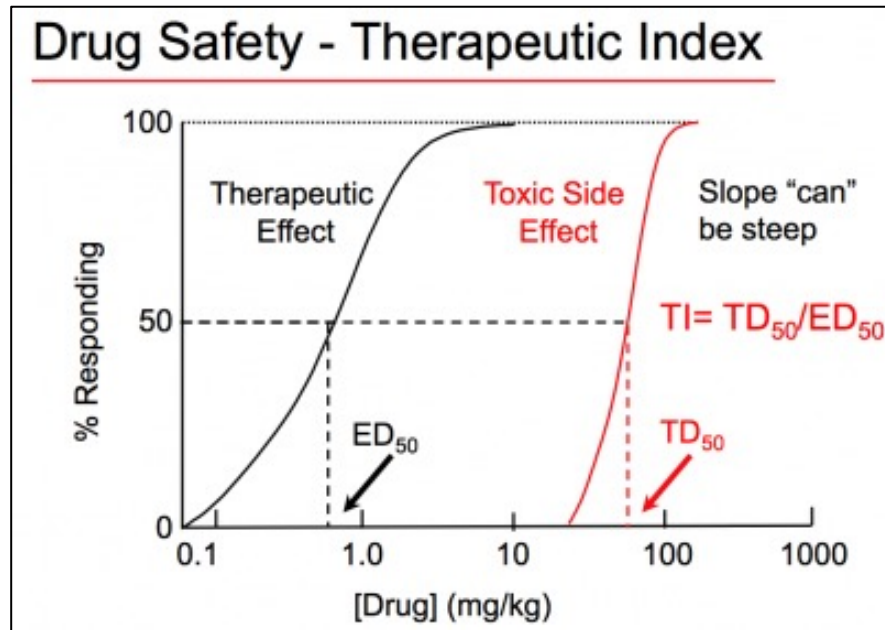


Paracelsus

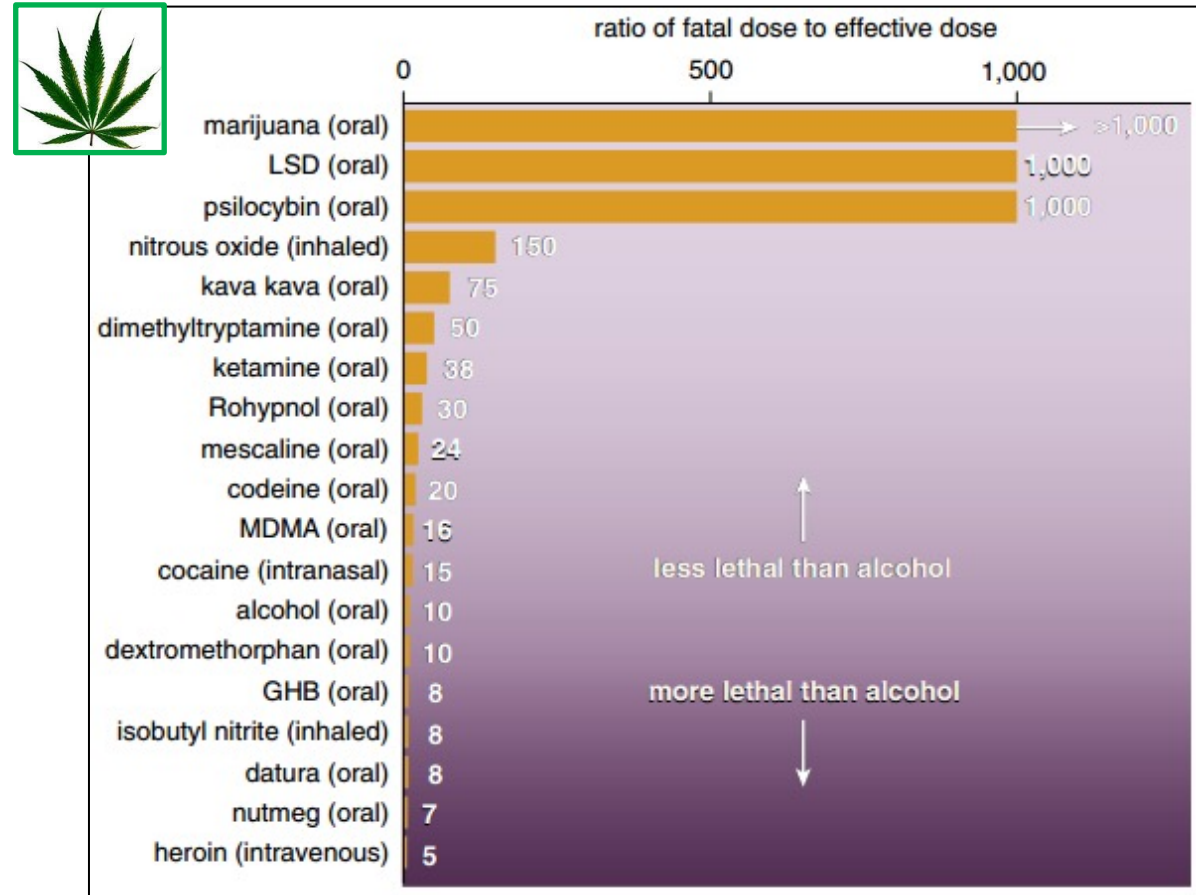
“All things are poison and nothing is without poison; only the dose makes a thing not a poison.”

www.chemicalsafetyfacts.org/dose-makes-poison-gallery/

Therapeutic Index Substances of Abuse



Toxicity of Recreational Drugs. *Am Sci.* 2006;94:206-208.



Substance Safety Ratios

Substance	Effective Dose	Lethal Dose	Safety Ratio	Dependence Potential
Opioids				
Heroin (IV)	8 mg	50 mg	6	Very high
Morphine (PO)	20 mg	300 mg	15	High
Sedatives				
Barbiturates Pentobarbital (PO)	250 mg	5 g	20	Moderate/high
Benzodiazepines Rohypnol (PO)	1 mg	30 mg	30	Moderate
Alcohol Ethanol (PO)	30 mg ³	300 mg	10	Moderate
Stimulants				
Caffeine (PO)	100 mg	10 g	100	Moderate/low
Cocaine (IN)	80 mg	1.2 g	15	Moderate/high
MDMA (PO)	125 mg	2 g	16	Moderate/low
Nicotine (INH)	1 mg	50 mg	50	High
Hallucinogens				
Ketamine (IV)	70 mg	2.7 g	38	Low
Nitrous oxide (INH)	3.5 liters	525 liters	150	Moderate/low
LSD (PO)	100 mcg	100 mg	1000	Very low
Mescaline (PO)	350 mg	8.4 g	24	Very low
Psilocybin (PO)	6 mg	6 g	1,000	Very low
Cannabis				
Marijuana (INH)	15 mg	> 15 g	> 1,000	Moderate/low

Gable. Drugs Soc. U.S. Public Policy. 2006:149-162.

politicsofsin.50megs.com/risk/Safety.Ratio-Dependence.Potential-Psychoactive.Drugs.html.

StreetTalk Meets PharmTalk

Pharmacological Properties Conducive to Substance Abuse

- High C_{\max} (large peak)
- Quick T_{\max} (fast onset)
- Receptor affinity (stronger magnet)
- Dopamine release (euphoria)

I Want It ALL

I Want It NOW

I Want Nothing Else

Ahhhhhh

Poison Center

1-800-222-1222

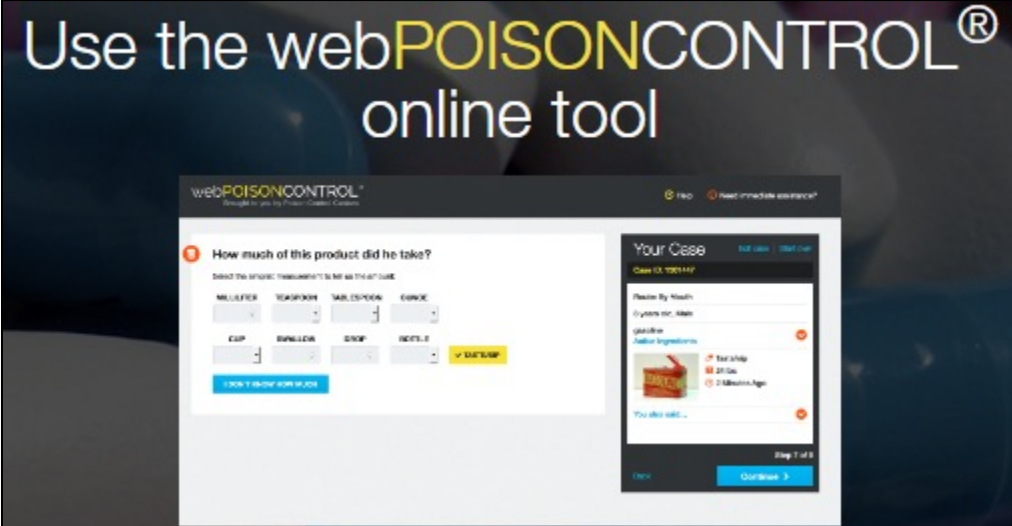
POISON CONTROL
National Capital Poison Center

Help & FAQ | Need immediate assistance? | Search

Poison & Prevention Info | Act Fast | The Poison Post® | Pill Identifier | Order Materials | Batteries | **DONATE NOW**

Call **POISON CONTROL** to
speak to an expert
1-800-222-1222

Use the web**POISONCONTROL**®
online tool



www.poison.org/.

Just Say NO



[www.scientificamerican.com/article/why-just-say-no-doesnt-work/.](http://www.scientificamerican.com/article/why-just-say-no-doesnt-work/)

7th Grade Spelling Bee Loss

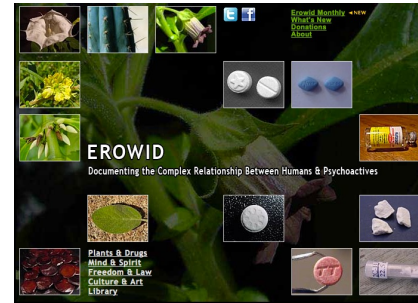
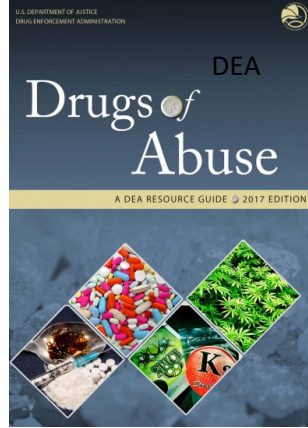


Just Say **KNOW**



www.scientificamerican.com/article/why-just-say-no-doesnt-work/.

Resources Concentrating on Illicit Substances

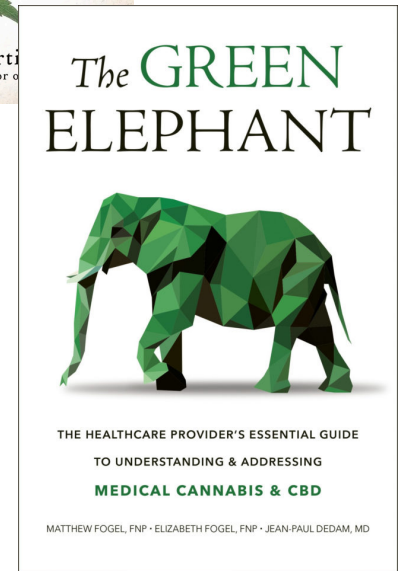
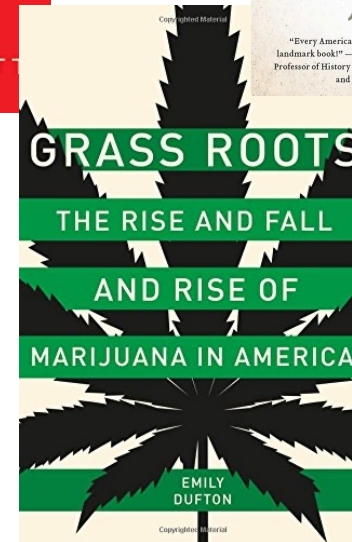
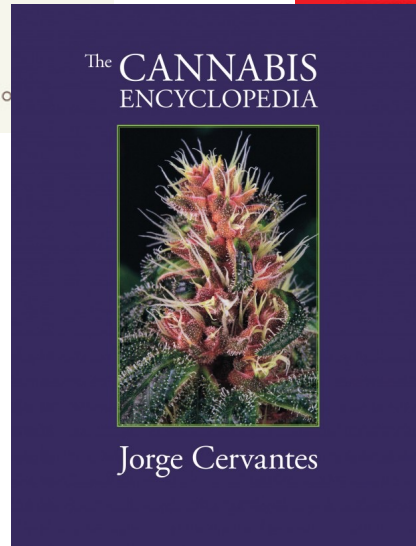
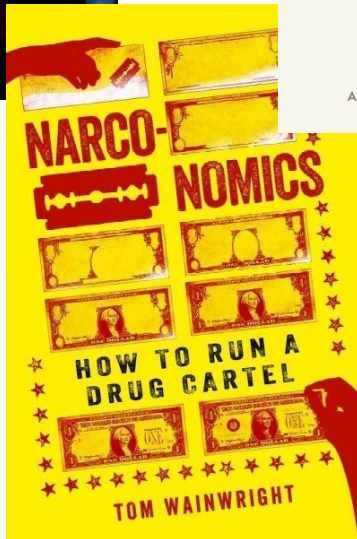
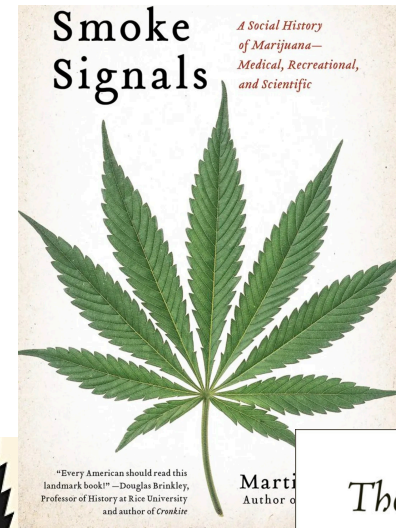
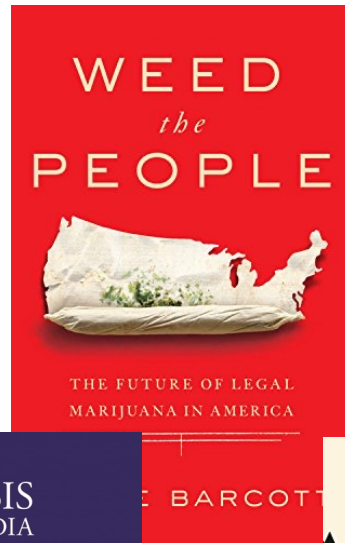
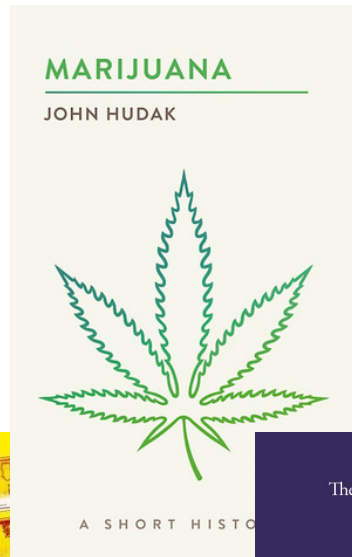
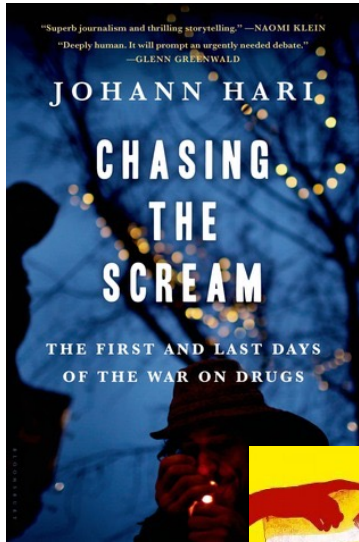


BLUELIGHT 

Drugs-Forum
the international drugs community

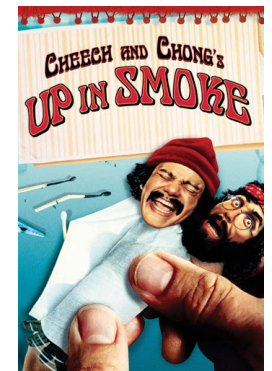
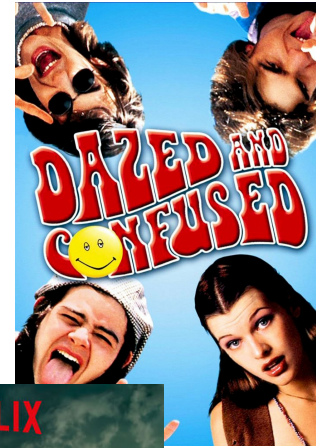


Papyrus Pot



www.ganjabpreneur.com/marijuana-books/

Marijuana Media



2005

1936

connect-bridgeport.com/connect.cfm?func=view§ion=News&item=An-Appearance-on-Netflixs-Recovery-Boys-Documentary-Allows-BHS-Alumna-Kelsey-Fogg-to-Share-Her-Own-Story-of-Recovery31591.

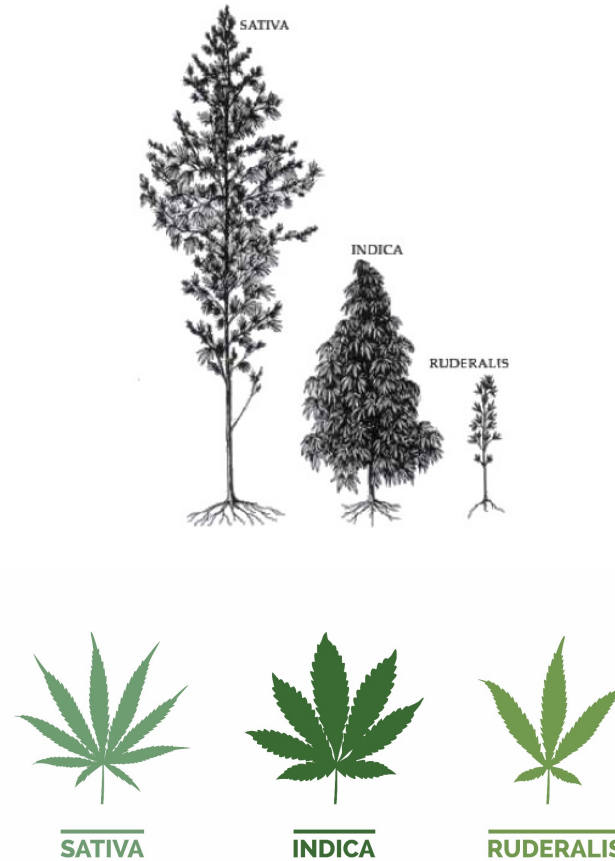
MEDICINAL MELODIES

Substances of Abuse	Song	Artist
DXM	Like a G6	Far East Movement
MDMA	We Can't Stop	Miley Cyrus
	We Found Love (Yellow Diamonds)	Rihanna
Cocaine	Master of Puppets	Metallica
	Cocaine	Eric Clapton
	Snow (Hey Oh)	Red Hot Chili Peppers
Meth(amphetamine)	Semi-Charmed Life	Third Eye Blind
Heroin	Mr. Brownstone	Guns N' Roses
	Mother's Little Helper	The Rolling Stones
	Brown Sugar	
Marijuana	Sister Morphine	
	Hits from the Bong	Cypress Hill
	Because I Got High	Afroman
	Gin & Juice	Snoop Dogg
	How High	Redman & Method Man
	Mary Jane	Rick James
	Dooo It	Miley Cyrus

Recreational and “Medical” Cannabis Coexisting

Cannabis Plants

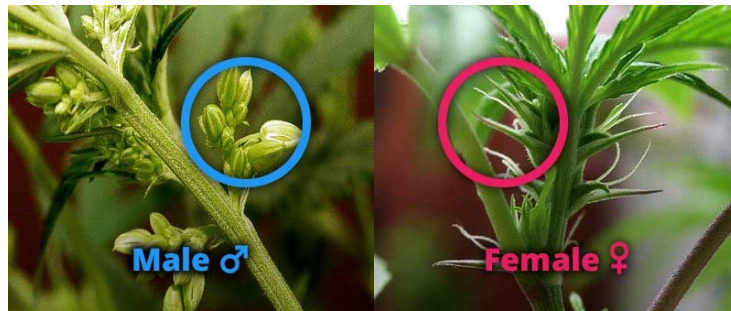
KINGDOM	-	Plantae
SUBKINGDOM	-	Viridiplantae
INFRAKINGDOM	-	Streptophytae
SUPERDIVISION	-	Embryophyta
DIVISION	-	Tracheophyta
SUBDIVISION	-	Spermatophytina
CLASS	-	Magnoliopsida
SUBCLASS	-	Hamamelididae
ORDER	-	Urticales
FAMILY	-	Cannabaceae
GENUS	-	Cannabis
SPECIES	-	Cannabis sativa



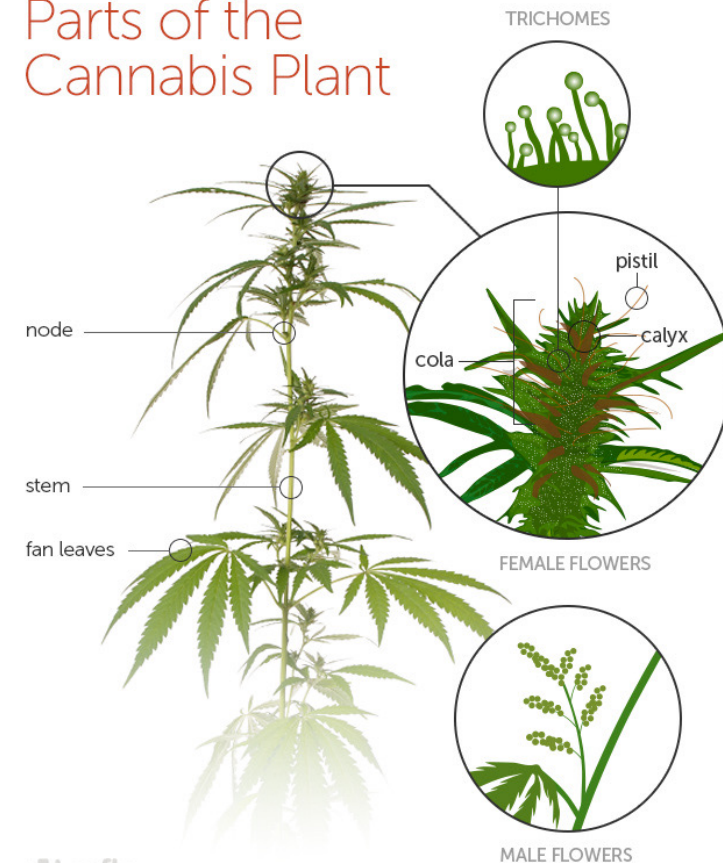
www.amaweed.com/en/blog/what-s-the-real-difference-between-hemp-and-weed/

The Cannabis Plant

- THC cultivation
 - Low grade: male and female plants
 - Med grade: fertilized females
 - High grade: isolated females
- Sinsemilla: “without seeds”



Parts of the Cannabis Plant



Punja. *Front Plant Sci.* 2020;June 25.
[www.merriam-webster.com/dictionary/sinsemilla.](http://www.merriam-webster.com/dictionary/sinsemilla)

General Guide

Indica strains are believed to be physically sedating, perfect for relaxing with a movie or as a nightcap before bed.

Sativas are said to provide invigorating, uplifting cerebral effects that pair well with physical activity, social gatherings, and creative projects.

Hybrids are thought to fall somewhere in between, offering a balance of indica and sativa effects.

A PERIODIC TABLE OF



EFFECT →

← **% THC**

← **ABBREVIATION**

← **COMMON USAGE**

COMMON USAGE

- P- pain
- D- depression
- I- insomnia
- LoA- loss of appetite
- N- nausea
- S- stress
- MC- menstrual cramps
- ADHD- adhd symptoms

← **General Effects**

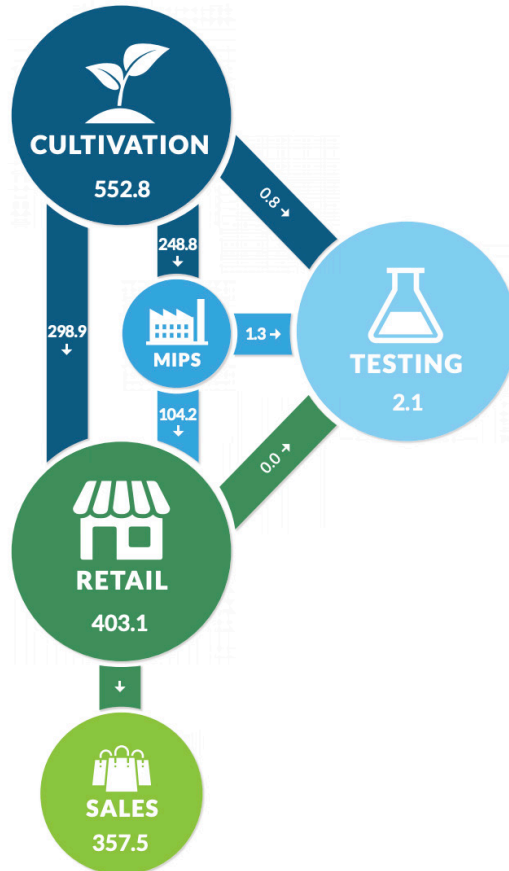
- C- creative
- E- energetic
- Eu- euphoric
- R- relaxing
- F- focused
- Sd- sedated

E, Eu 23% Ag Acapulco Gold D, LoA, N	Eu, R 27% OGk OG Kush R, LoA, N	Eu, F 28% Aw Alien Wreath S, N	C, R, Sd 23% 9ph 9 Pound Hammer D, R, N	Eu, S 20% Afg Afgoosey D, I, N	Eu, C 22% Bwh Berry White D, LoA, N	R, C, Sd 24% Bbr Blueberry I, R, A						
E, F 25% Ah Amnesia Haze R, LoA, D	C, E, Eu 25% B11 Boy 11 S, LoA	C, E 22% Ch Chocolate D, R, A	S, R, Eu 25% Gra Grape Ape D, R, N	C, Sd, R 23% Gdd Granddaddy Purple R, I, N	Eu, H, S 24% G13 G13 D, LoA, N	Sd, R, S 23% Buk Bubba Kush D, LoA, N						
C, E, U, E 28% Oc Orange Crush D, R, A	Eu, E 28% Dg Dirty Girl D, N	E, F 26% Db Durban Poison D, LoA, N	Eu, C 25% Gth Ghost Train Haze D, LoA, N	C, R 32% Hrj Herijuana D, R, I	Eu, S, R 20% Hku Hindu Kush D, P, A	Eu, R, F 25% Ing Ingrid D, LoA, N	S, R 20% Kku Kosher Kush D, A, P					
Eu, F, C 20% Gf Grapefruit A, LoA, P	Eu, C 24% Gc Green Crack D, LoA, N	R, E, S 25% Lh Lemon Haze N	C 21% Acdc ACDC A, D, P	C, R 20% Ak AK-47 R, LoA, I	Sd, S, C 25% Bog Banana OG D, A, N	E, C, R 27% Bd Blue Dream R, LoA, A	Eu, R 6% Cnn Cannonic R, LoA, N	Eu, R 22% Cd Cherry OG D, LoA, N	H, E 22% Chb Cherry Bomb D, S, P	S, Sd 26% Cp Cherry Pie A, ADHD, I	Eu, C 20% Mku Master Kush D, LoA, N	Eu, C 20% Lvh Lavender Haze D, LoA, P
Sd, R, C 22% Lbu Laughing Buddha D, R, N	C, E 19% Mw Maui Wowie R, LoA, A	Eu, E, C 16% Pr Panama Red D, LoA, N	E, F 22% Cin Cinderella 99 D, A, P	R, H, F 9% Dh Dancehall D, R, S	Eu, C 26% Ddr Double Dream D, LoA, P	Eu, C, R 30% Dtt Dutch Treat I, LoA, A	Eu, R 19% Ew Ewok D, I, P	C, R 23% Fr Fruity Pebbles D, LoA, N	C, Sd 25% Ge Gelato D, R, N	E, C 23% Gg Golden Goat A, LoA, N	Eu, Sd, E 33% Nli Northern Lights D, LoA, N	R, C, Eu 21% Oku Obama Kush D, I, P
E, F, Eu 24% Sbc Strawberry Cough R, LoA, A	E, Eu, F 25% Slh Super Lemon Haze A, LoA, N	E, C 23% Ssh Super Silver Haze D, LoA, A	Eu, R, F 27% Hb Headband D, LoA, P	E, C 25% Jg Jeon Gyu D, LoA, N	Eu, C 21% Jbn Jillybean I, A, N	Eu, E, F 20% Jf Juicy Fruit A, R, N	Eu, R 24% Lry Larry OG D, A, N	C, S 21% Le Lemon Kush D, LoA, N	H, E, C 28% Ldi Lodi Dodi R, ADHD, A	Sd, R 24% Mku Mango Kush D, LoA, N	Eu, R 20% Pby Plushberry D, LoA, N	Eu, F, R 27% Pz Pez I, A, P
Eu, C 24% Jh Jack Herer A, LoA, N	C, E 15% Km Kali Mist D, LoA, N	R, C 28% Bw Black Widow D, LoA, P	Eu, R 20% Mpu Mendocino Purps D, A, I	E, F 26% Mfk Middlefork A, LoA, ADHD	C, Sd, S 26% Lk Lemon Kush D, LoA, N	C, E 18% Pf Permafrost R, LoA, A	S, R 26% Pi Pineapple Chunk D, I, N	E, Eu 27% Px Pineapple Express D, LoA, N	S, Sd, R 27% Pku Pink Kush D, R, N	H, R, E 19% Rk Rokk OG D, S, P	R, Sd 35% Qur Querkie D, LoA, N	R, F, C 26% Prd Presidential OG D, R, I
C, F 22% Wn Willie Nelson D, LoA, N	E, R, H 18% Sch Schrom S, P, D	E, Eu 25% Sd Sour Diesel D, LoA, P	Eu, Sd 10% Sts Sour Tsunami D, LoA, P	R, E, F 27% Sr Sour OG D, LoA, P	H, R 24% Scp Snowcap D, S, N, M	Eu, C, Sd 25% Snd Snoop's Dream D, LoA, N	R, C 22% Sk1 Skunk No. 1 D, I, N	S, Eu, Sd 27% Ogk OG Kush D, LoA, N	Eu, Sd 19% Sfv SPV OG D, LoA, N	E, C 25% Sa Sage D, LoA, N	R, F 23% Zki Zkittlez D, LoA, N	Eu, S 21% Wwr Willy's Wonder R, LoA, A
C, F 22% Ta Tangie R, A, N	E, Eu, C 20% Ph Purple Haze R, A, N	Eu, R 21% Is Island Sweet Skunk D, LoA, P	Eu, C 16% Sq Space Queen D, R, A	Eu, C 24% Ssb Sunset Sherbert D, S, A	Eu, Sd 21% Tah Tahoe OG D, R, A	Eu, C, R 21% Tad Tangerine Dream R, A, I	Eu, R 18% Twr Trainwreck D, LoA, N	Eu 18% UK UK Cheese D, LoA, N	E, Eu, F 25% Wf White Fire OG A, LoA, P	E, Eu 20% Wwi White Widow R, A, N	F, C 24% Xj XC-13 D, LoA, A	R, S, Sd 21% Afg Afghani I, A, N

Design by Christopher Williams

Marijuana Flower Testing and Sales

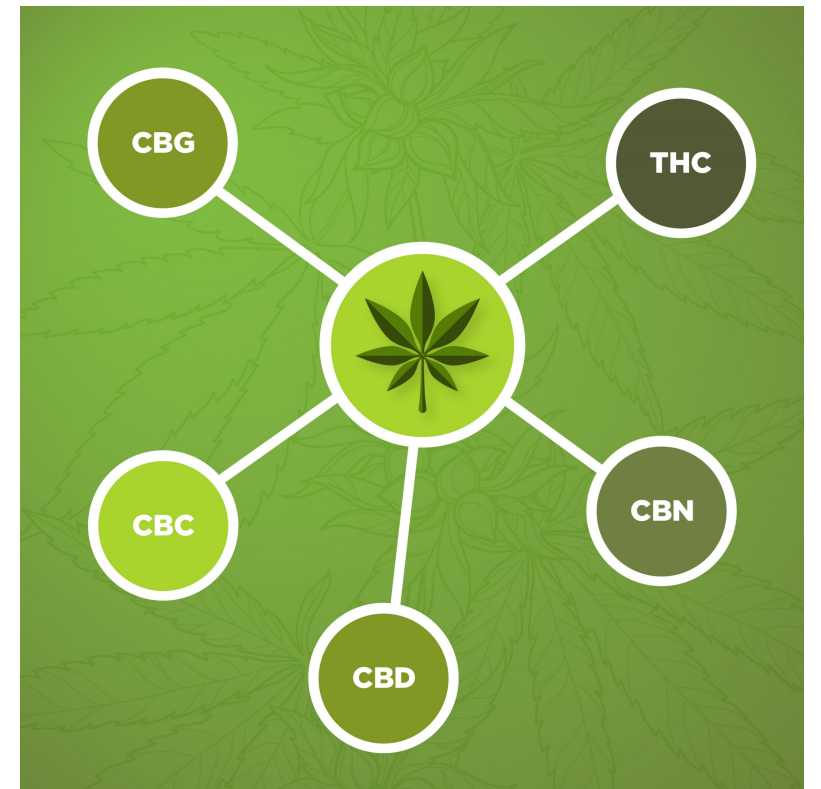
Transfer Flows of Flower Equivalent, 2019



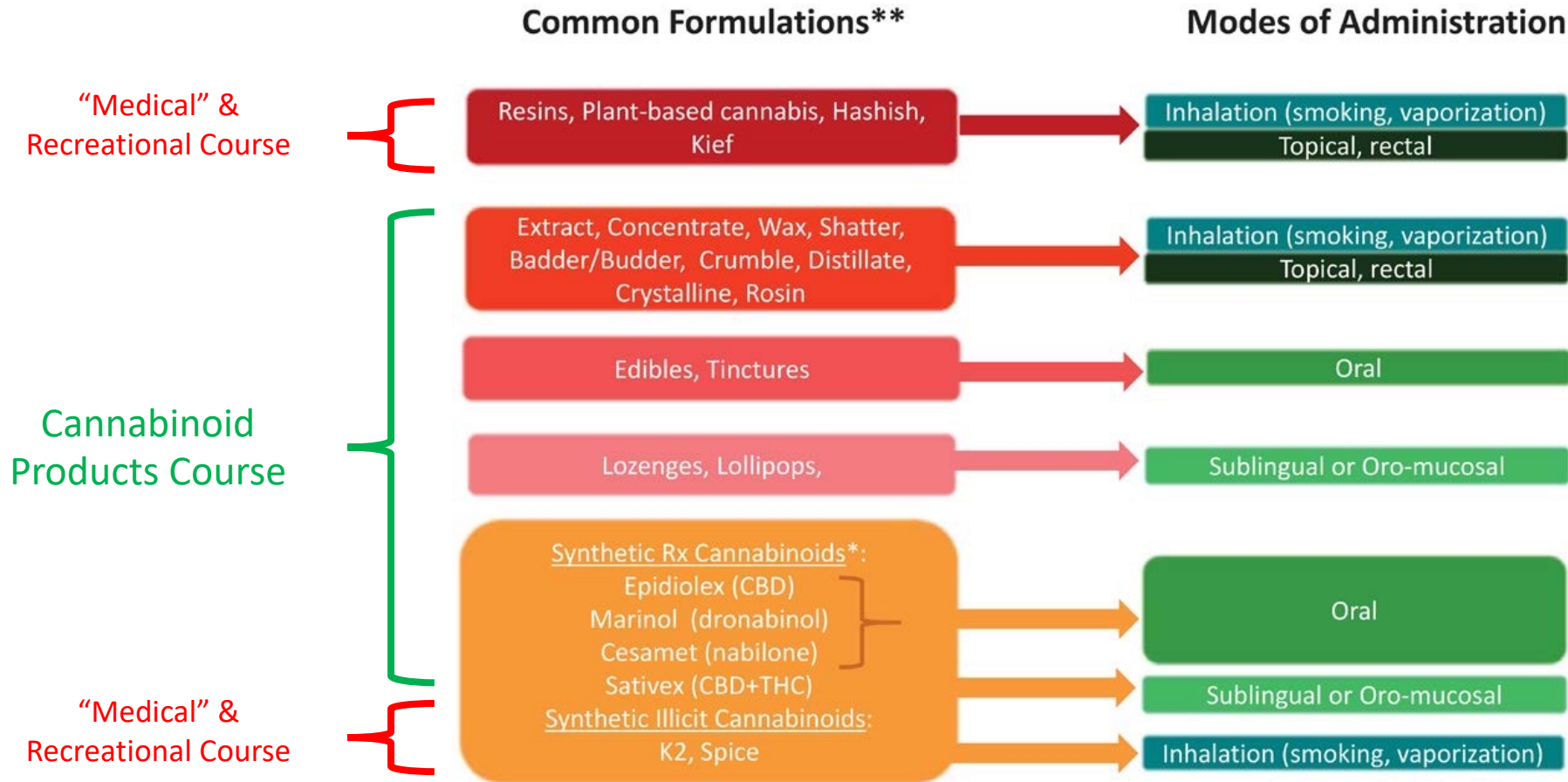
Then again, are
FDA-approved products
retested at a greater frequency?



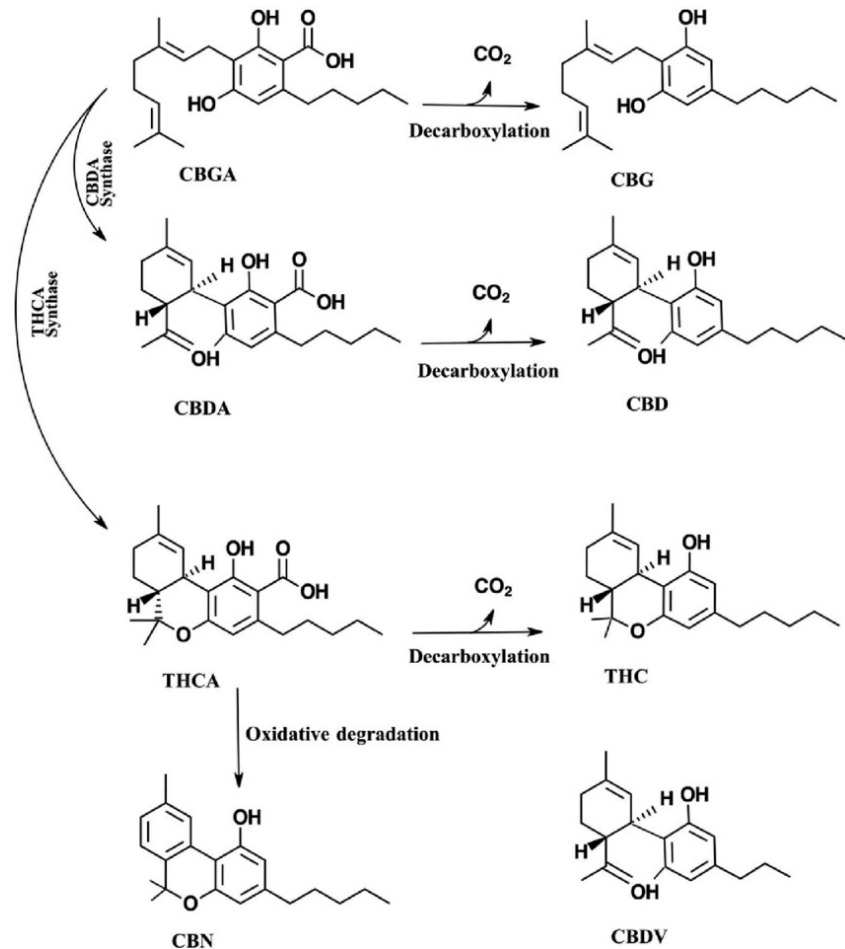
Cannabinoids



Cannabis Formulations and Administrations



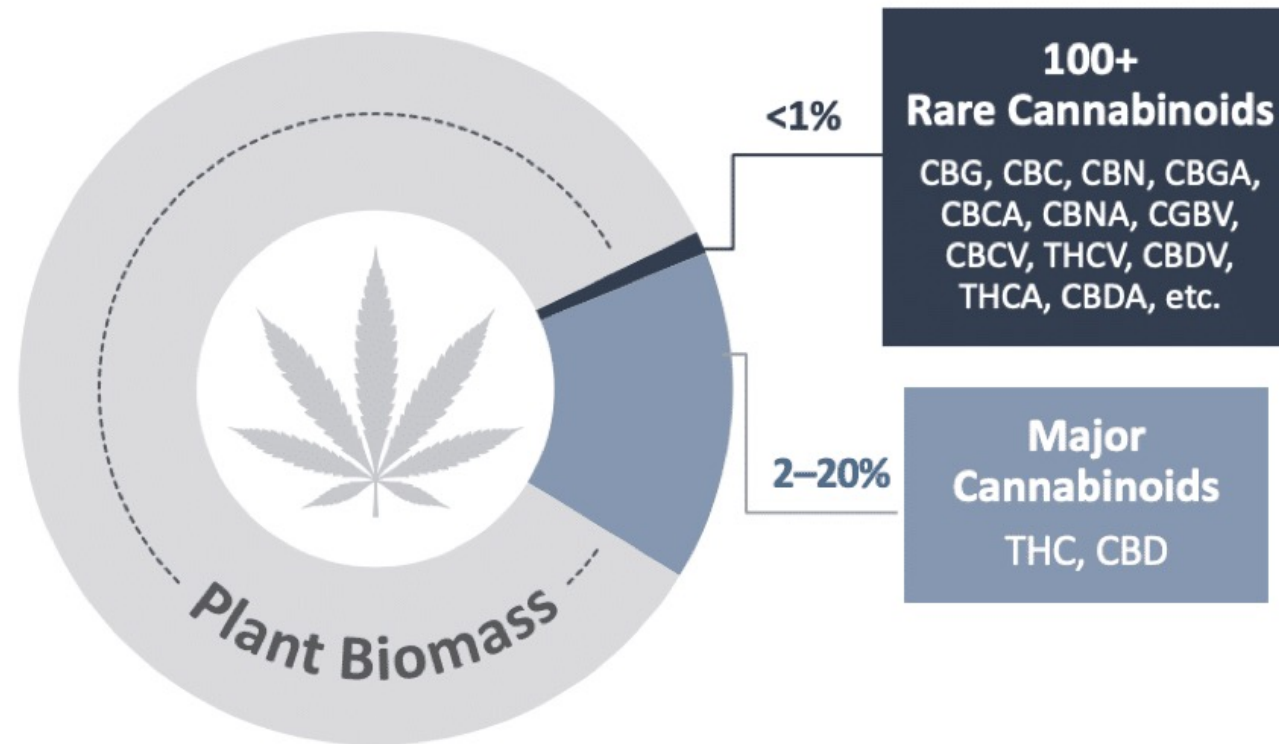
Cannabis Biosynthesis and Conversion of Cannabinoids



- CBGA: cannabigerolic acid
- CBG: cannabigerol
- CBDA: cannabidiolic acid
- CBD: cannabidiol
- THCA: tetrahydrocannabinolic acid
- THC: tetrahydrocannabinol
- CBN: cannabinol
- CBDV: cannabidivarin

www.researchgate.net/figure/Major-cannabinoids-present-in-Cannabis-sativa-L-Biosynthesis-and-conversion-pathways_fig1_332566538.

A Pot Full of Cannabinoids



www.inmedpharma.com/media-news/cannabinol-101-the-science-of-cannabinol-cbn/

Tetrahydrocannabinol (THC)

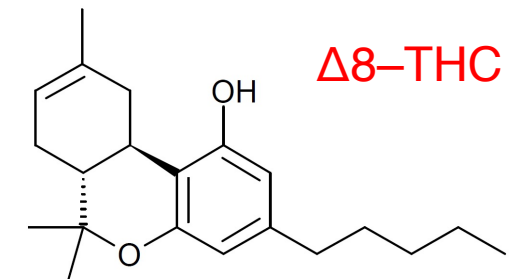
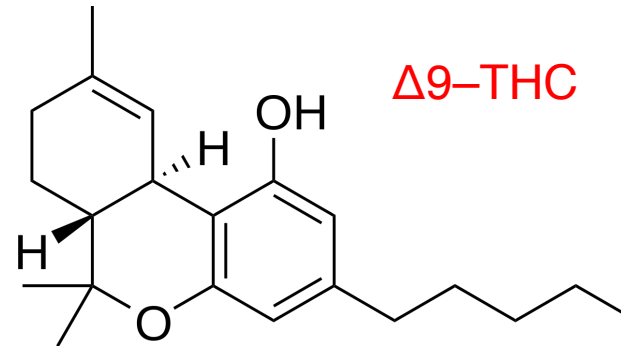
- Δ^9 -tetrahydrocannabinol
 - Δ^8 -tetrahydrocannabinol also exists

- Mechanism of action
 - CB1 partial agonist

- Inhalation: immediate absorption

- Oral ingestion: effects delayed (30 minutes to 1 hour)

- Highly lipophilic
 - Distributing rapidly to highly perfused tissues, and later to fat tissue

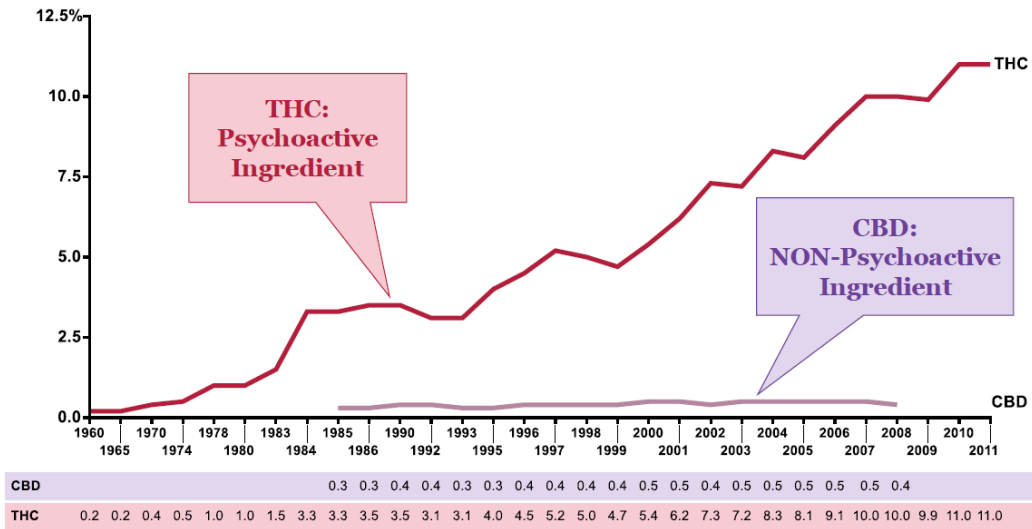


Horn. Drug Interactions with Marijuana. *Pharmacy Times*. Dec 2014.
Bridgeman. *P T*. 2017;42(3):180-188.

Trends: THC Potency and Emergency Room Visits

Marijuana has become significantly more potent since the 1960s

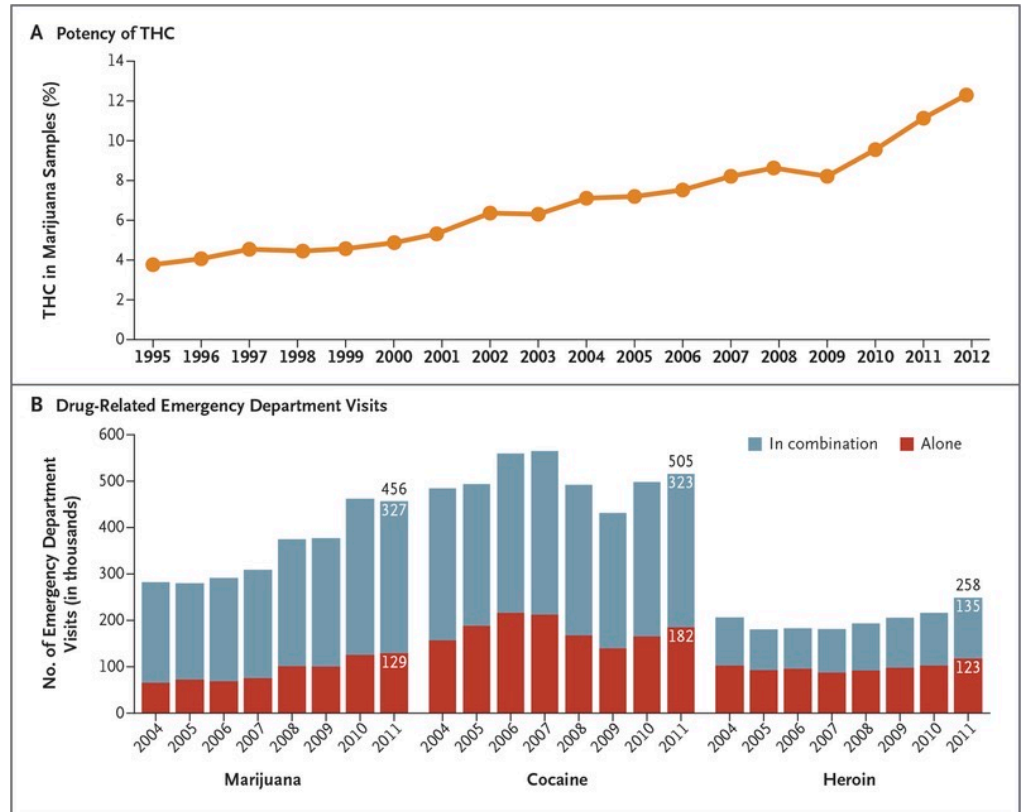
Average THC and CBD levels in the United States



© SAMHSA

Source: Mehmedic et al., 2010

13



Volkow. *N Engl J Med.* 2014;370:2219-2227.

Marijuana THC Potency

- Typical joint: 0.5 grams of marijuana
 - 1960's to 1980's joint (2% THC) → 10 mg THC per joint
 - 2020's joint (10% THC) → 50 mg THC per joint
 - 2020's extracts (90% THC) → 450 mg THC (relatively)
- One nabiximols spray: 2.7 mg THC and 2.5 mg CBD
- Cocaine: coca leaf vs crack
- Nicotine: FDA considering reducing tobacco nicotine concentrations
- Ethyl alcohol ABV: difference between beer/wine (4) and bourbon (40)
- Opioid MME factors: codeine (0.15) vs carfentanyl (10,000)



Volkow. *N Engl J Med.* 2014;370:2219-2227.

nypost.com/2019/02/11/mike-tyson-smokes-huge-joint-at-weed-festival/.

Stuyt. *Mo Med.* 2018;115(6):482-486.

Dumont. *Ned Tijdschr Geneeskd.* 2020;164:D4578.

Tetrahydrocannabinol (THC)

Timing of Effects

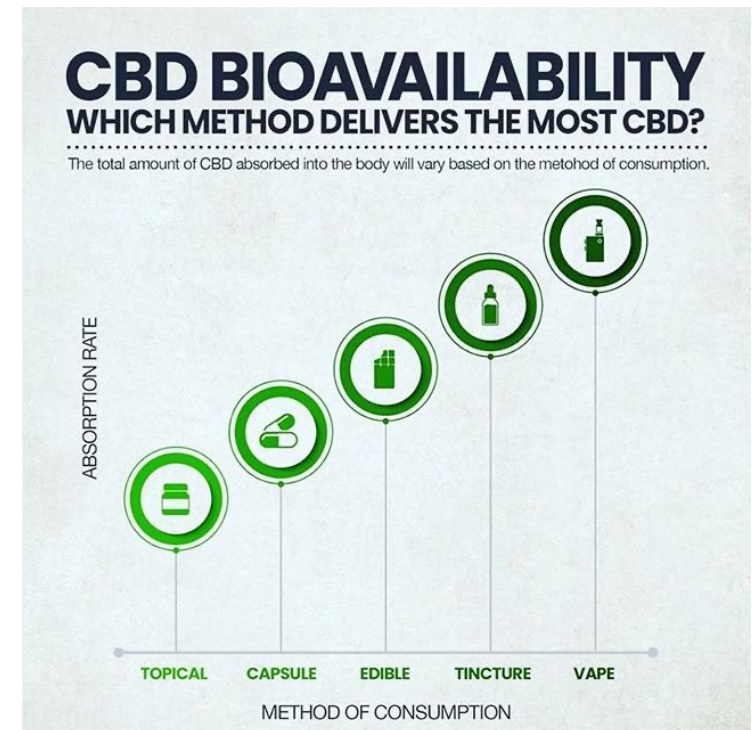
- Inhalation
 - Immediate absorption
 - Peak 15 to 30 minutes
 - Taper off in 2 to 3 hours
- Oral ingestion
 - Effects delayed (30 minutes to 1 hour)
 - Peak 2 to 3 hours
 - Taper off in ~12 hours



Horn. Drug Interactions with Marijuana. *Pharmacy Times*. Dec 2014.
Bridgeman. *P T*. 2017;42(3):180-188.

Marijuana THC Absorption

- Cigarette: 10% to 20%
- Pipe: 40% to 50%
- Water pipe (bong): ~100%
- Vape: ~100% (no smoke irritation)
- Edibles.....delayed ~1 hour



Mayo Clinic Proceedings 2019;94:1840-1851.

www.practicalpainmanagement.com/treatments/pharmacological/how-communicate-medical-marijuana-dispensary.

Tetrahydrocannabinol (THC)

Combustible Products

- Joint

- Small and portable
- Cannabis rolled up inside a thin rolling paper
- Often have a crutch, or filter, which adds stability to the roll and allows smoking to the end without burning fingertips

- Blunt

- A roll with cannabis inside a cigar or blunt wrap
- Wraps are made out of tobacco (stimulant effect)
- Typically, bigger than joints and last a lot longer

- Spliff

- Like a joint, but has tobacco and cannabis mixed together in a rolling paper, typically with a crutch/filter
- Allows personalization of tobacco:cannabis ratio
- Europe: “joint” refers to cannabis/tobacco combo (eg, joining)



[www.leafly.com/news/cannabis-101/whats-the-difference-between-joints-blunts-and-spliffs.](http://www.leafly.com/news/cannabis-101/whats-the-difference-between-joints-blunts-and-spliffs)

Tetrahydrocannabinol (THC)

Combustible Products

- Paper
 - Amount of cannabis
 - Size of the paper
 - Flavor
 - Tobacco papers are notably sweeter than hemp paper
 - Burn
 - Thicker papers burn slower than thinner papers
 - Hemp, rice, paper, etc
- Paper protectors
 - Enable travel with papers for future rolling



www.leafly.com/news/cannabis-101/whats-the-difference-between-joints-blunts-and-spliffs.

Tetrahydrocannabinol (THC)

Hashish and Hash Oil/Extracts

- Hashish

- Isolated marijuana resin
- Dark colored gummy balls



- Hash oil and extracts

1. Boil plant
2. Filter out solids
3. Vaporize all water
4. Leaving hash oil



www.merriam-webster.com/dictionary/hashish..
[en.wikipedia.org/w/index.php?title=Hash_oil&oldid=1043980711.](http://en.wikipedia.org/w/index.php?title=Hash_oil&oldid=1043980711)

Can you SPOT the POT?



DEA

U.S. Drug Enforcement Administration

Teen Vaping



TEEN VAPING CLIMBS SIGNIFICANTLY*

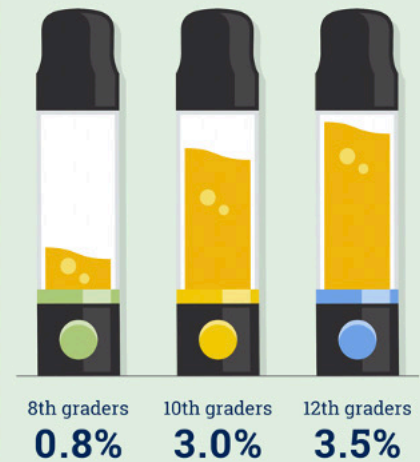
THC VAPING

Past month use



DAILY THC VAPING

Measured for the first time in 2019



*2018 – 2019 INCREASE IS THE SECOND LARGEST ONE-YEAR JUMP EVER TRACKED FOR ANY SUBSTANCE IN THE 45-YEAR SURVEY HISTORY (NICOTINE VAPING WAS THE LARGEST FROM 2017 – 2018)

www.drugabuse.gov/drug-topics/trends-statistics/infographics/monitoring-future-2019-survey-results-vaping.
www.drugabuse.gov/news-events/news-releases/2019/12/vaping-of-marijuana-on-the-rise-among-teens.

History Repeating Itself...



JUUL



AB InBev

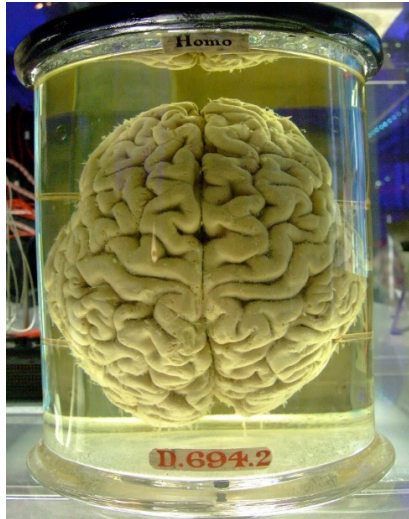


Laced Marijuana

Love Boat: Marijuana laced with formaldehyde

KD: Marijuana or tobacco laced with bug spray (pyrethroids)

When you're out of papers and
your bowl is broken



www.indystar.com/story/news/crime/2018/03/18/think-what-its-doing-your-brain-using-bug-spray-get-high/426668002/

Street Synthetic Marijuana

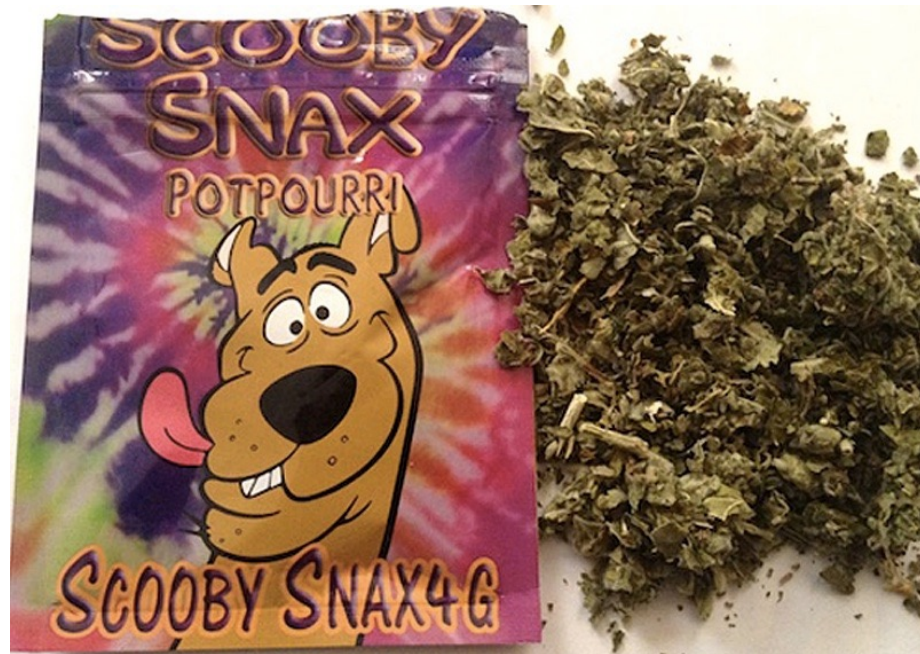
Street Synthetic Marijuana Nicknames



- Scooby Snax
- K2
- Spice
- Legal Funk
- Arizona
- Black Mamba
- Bombay Blue
- Genie
- Banana Ice Cream
- Nuke
- Krypton
- Lava Red



The Scooby Snack Market



Synthetic Cannabinoids

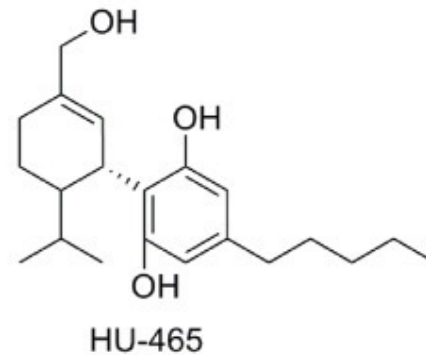
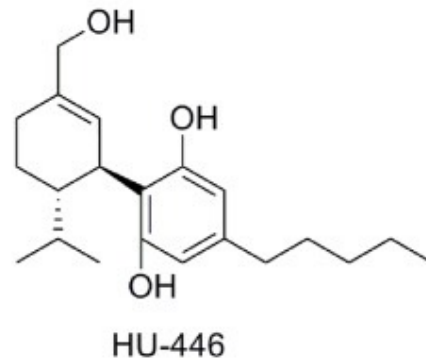
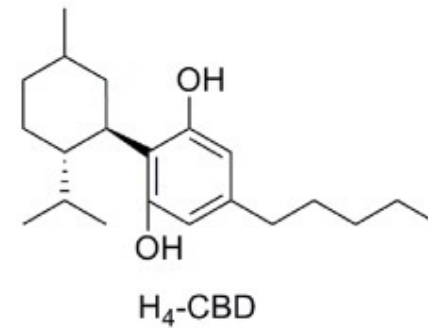
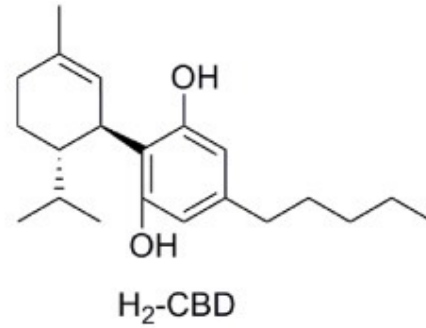
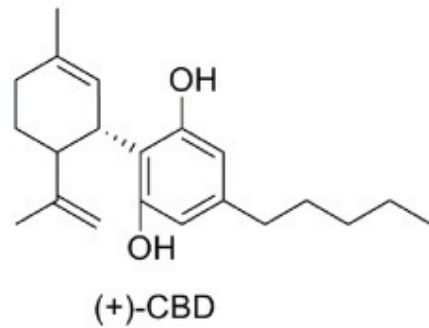
CBD Derivatives

- Hydrogenated
- Dimethylheptyl (DMH)
- C4'-alkyl chain modifications
- Halogenated (Cl, Br, Fl, & I)
- Hydroxyl
- Diacetylated
- Quinones



CBD Derivatives

Hydrogenated

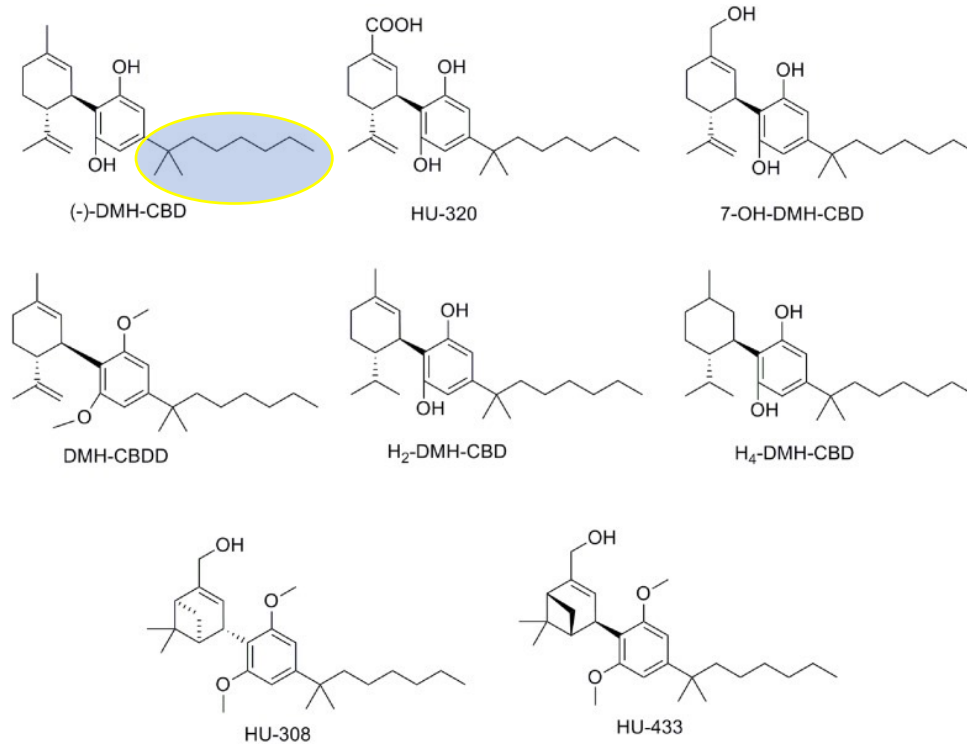


CB1 and CB2 Agonists (Preferential to CB1)

Morales. *Front Pharmacol.* 2017;8:422.

CBD Derivatives

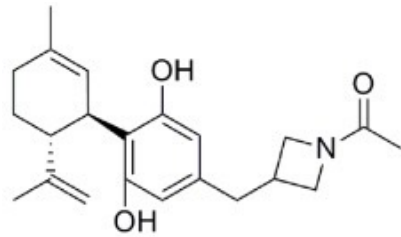
Dimethylheptyl (DMH)



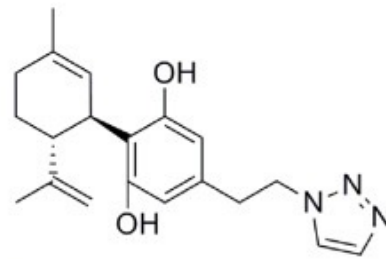
- DMH improves CB1 receptor affinity
- HU-308/422: peripheral CB₂-selective agonists

CBD Derivatives

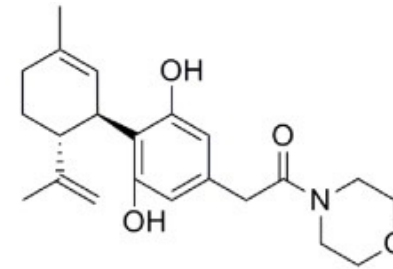
C4'-Alkyl Chain Modifications



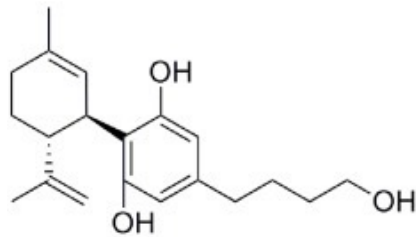
KLS-13019



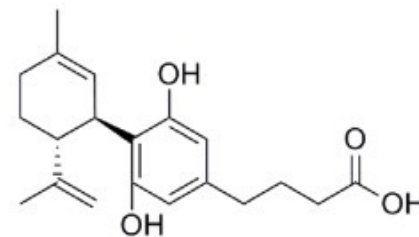
4'-[2-(1H-1,2,3-Triazolyl)ethyl]-CBD



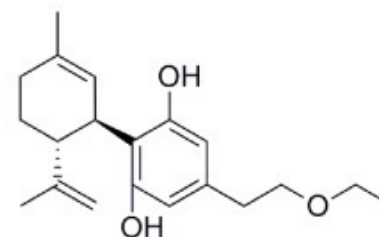
4'-(2-Morpholinoethyl)-CBD



4'-(4-Hydroxybutyl)-CBD



4'-(3-Carboxypropyl)-CBD



4'-(2-Ethoxyethyl)-CBD

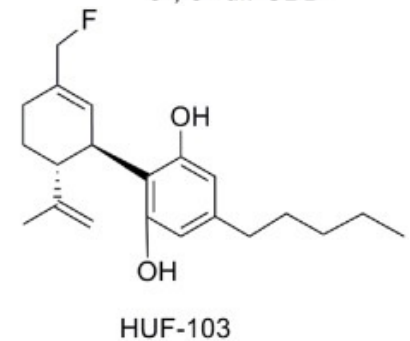
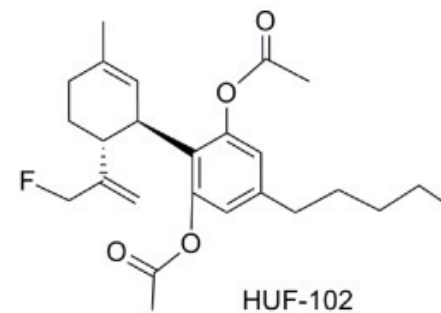
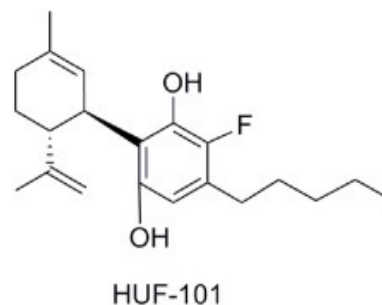
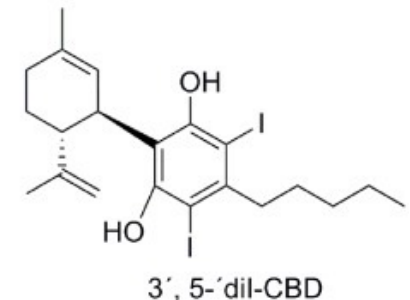
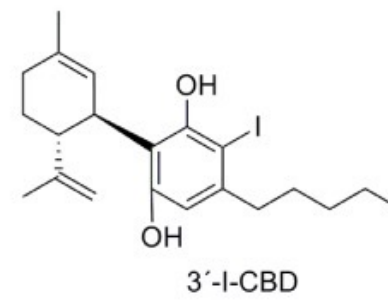
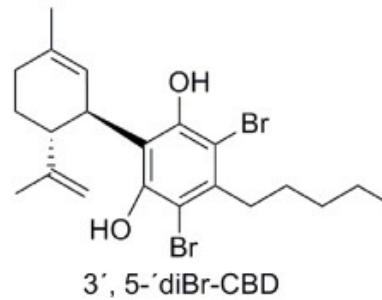
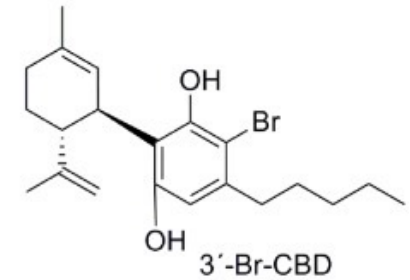
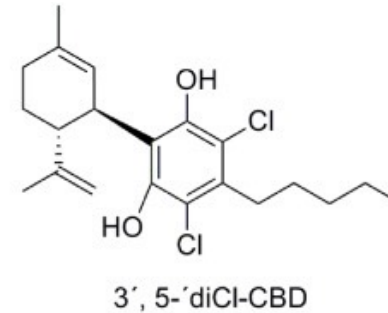
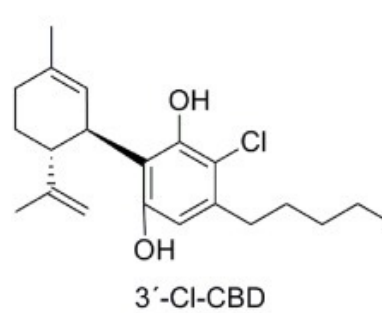
- Structural modifications change “drug-likeness”
 - # H-bond donors, acceptors, and polar surface area
- KLS-13019
 - 50x potency and 400x safety compared to CBD

CBD Derivatives

Halogenated (F, Cl, Br, and I)

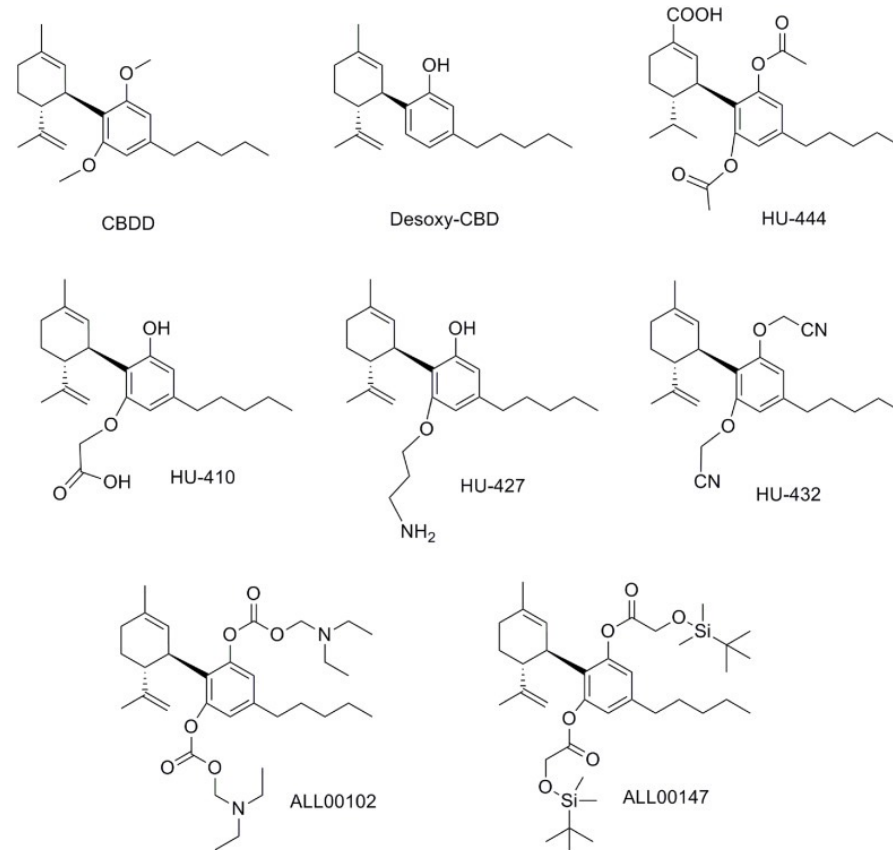
- Mono-halogenated
 - Activity similar to CBD
- Di-halogenated
 - Lower activity than CBD

1 H Hydrogen	2 He Helium																														
3 Li Lithium	4 Be Beryllium	5 B Boron	6 C Carbon	7 N Nitrogen	8 O Oxygen	9 F Fluorine	10 Ne Neon																								
11 Na Sodium	12 Mg Magnesium	13 Al Aluminum	14 Si Silicon	15 P Phosphorus	16 S Sulfur	17 Cl Chlorine	18 Ar Argon																								
19 K Potassium	20 Ca Calcium	21 Sc Scandium	22 Ti Titanium	23 V Vanadium	24 Cr Chromium	25 Mn Manganese	26 Fe Iron	27 Co Cobalt	28 Ni Nickel	29 Cu Copper	30 Zn Zinc	31 Ga Gallium	32 Ge Germanium	33 As Arsenic	34 Se Selenium	35 Br Bromine	36 Kr Krypton														
37 Rb Rubidium	38 Sr Strontium	39 Y Yttrium	40 Zr Zirconium	41 Nb Niobium	42 Mo Molybdenum	43 Tc Technetium	44 Ru Ruthenium	45 Rh Rhodium	46 Pd Palladium	47 Ag Silver	48 Cd Cadmium	49 In Indium	50 Sn Tin	51 Sb Antimony	52 Te Tellurium	53 I Iodine	54 Xe Xenon														
55 Cs Cesium	56 Ba Barium	57 La Lanthanum	58 Ce Cerium	59 Pr Praseodymium	60 Nd Neodymium	61 Pm Promethium	62 Sm Samarium	63 Eu Europium	64 Gd Gadolinium	65 Tb Terbium	66 Dy Dysprosium	67 Ho Holmium	68 Er Erbium	69 Tm Thulium	70 Yb Ytterbium	71 Lu Lutetium	72 Hf Hafnium	73 Ta Tantalum	74 W Tungsten	75 Re Rhenium	76 Os Osmium	77 Ir Iridium	78 Pt Platinum	79 Au Gold	80 Hg Mercury	81 Tl Thallium	82 Pb Lead	83 Bi Bismuth	84 Po Polonium	85 At Astatine	86 Rn Radon
87 Fr Francium	88 Ra Radium	89 Ac Actinium	90 Th Thorium	91 Pa Protactinium	92 U Uranium	93 Np Neptunium	94 Pu Plutonium	95 Am Americium	96 Cm Curium	97 Bk Berkelium	98 Cf Californium	99 Es Einsteinium	100 Fm Fermium	101 Md Mendelevium	102 No Nobelium	103 Lr Lawrencium	104 Rf Rutherfordium	105 Db Dubnium	106 Sg Seaborgium	107 Bh Bohrium	108 Hs Hassium	109 Mt Meitnerium	110 Ds Darmstadtium	111 Rg Roentgenium	112 Cn Copernicium	113 Nh Nihonium	114 Fl Flerovium	115 Lv Livermorium	116 Ts Tennessine	117 Og Oganesson	



CBD Derivatives

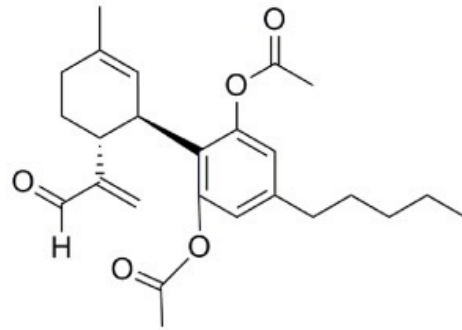
Hydroxyl



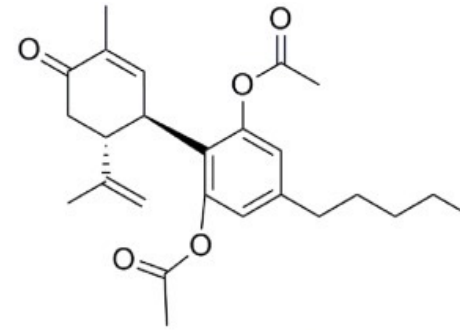
- Improved solubility, stability, and bioavailability parameters compared to CBD

CBD Derivatives

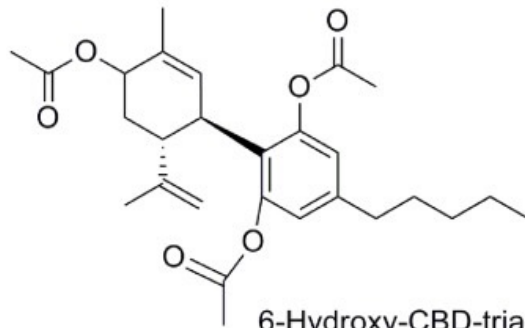
Diacetylated



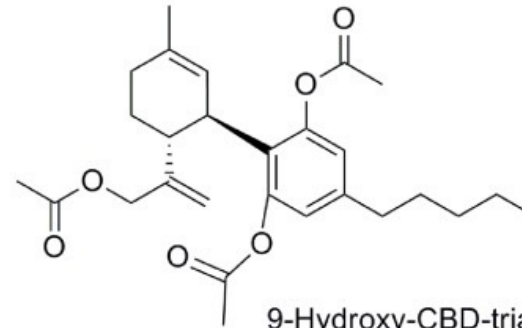
CBD-aldehyde-diacetate



6-Oxo-CBD-diacetate



6-Hydroxy-CBD-triacetate

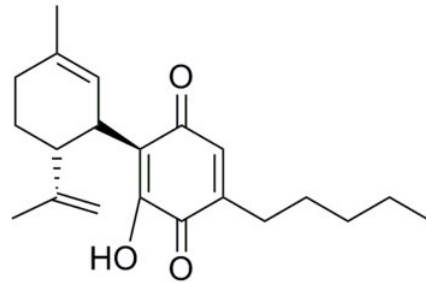


9-Hydroxy-CBD-triacetate

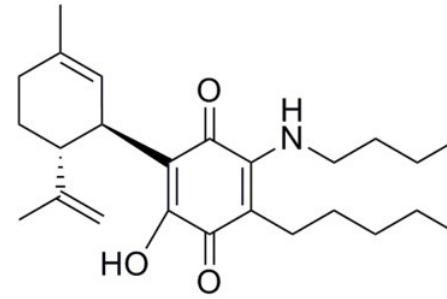
- Safety, efficiency, and potency of these 4 compounds were lower than that of CBD
- Diacetylated CBDs could potentially act as “prodrugs” to CBD (via deacetylation)

CBD Derivatives

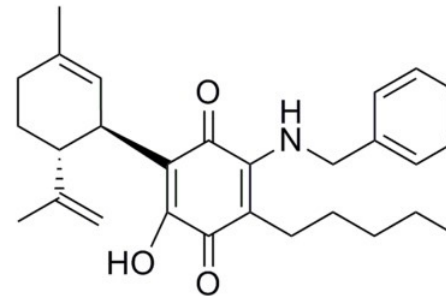
Quinones



HU-331



CBD-Q (V)



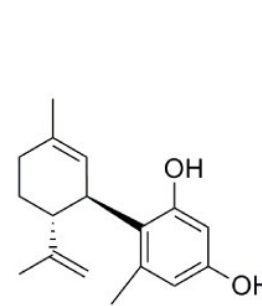
CBD-Q (VIII)

- PPAR γ agonists
- Studied in cancer treatment

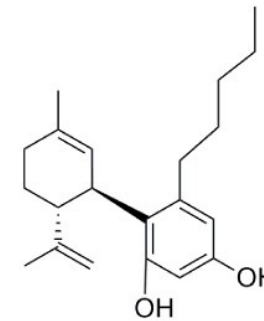
CBD Derivatives

Miscellaneous

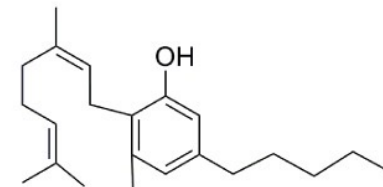
- O-1602
 - GPR18 Biased Agonist (possibly GPR 55)
- Abn-CBD
 - Possible targets: GPR55 and GPR18
- CBG
 - Cannabinoid precursor
- Cannabimovone
 - Weak TRPV1 agonist



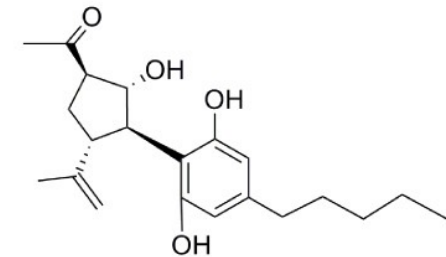
O-1602



Abn-CBD



CBG



Cannabimovone

Synthetic Cannabinoids

THC Derivatives

- 1st Generation
 - Sterling-Winthrop Aminoalkylindoles (WIN-X)
 - John Williams Huffman (JWH-X)
 - Hebrew University (HU-X)
 - Charles Pfizer (CP-X)
- 2nd Generation
 - Alkyl derivatives
 - N-methylpiperidines
 - Benzoindoles
- 3rd Generation
 - Indoles
 - Indazoles



Synthetic Cannabinoids

Sterling-Winthrop Aminoalkylindoles (WIN-X)

Win 48,098 (pravadoline)

- 1st of the researched analgesics distinct from opioid/COX activity
- NSAID structure (~indomethacin)
- Morpholinoethyl group binds to CB receptors similar to THC
- Research dropped due to nephrotoxicity and stigma of cannabinoid activity

WIN 55,212-2

- CB1 agonist
- Research dropped due to nephrotoxicity and stigma of cannabinoid activity

WIN 55,225 (JWH-200)

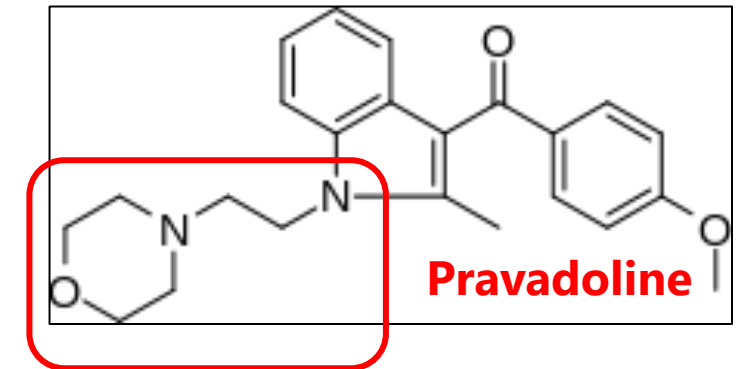
- CB1 agonist

WIN 54,461 (6-bromopravadoline)

- CB2 agonist

WIN 56,098

- CB2 antagonist
- Tricyclic aryl derivative



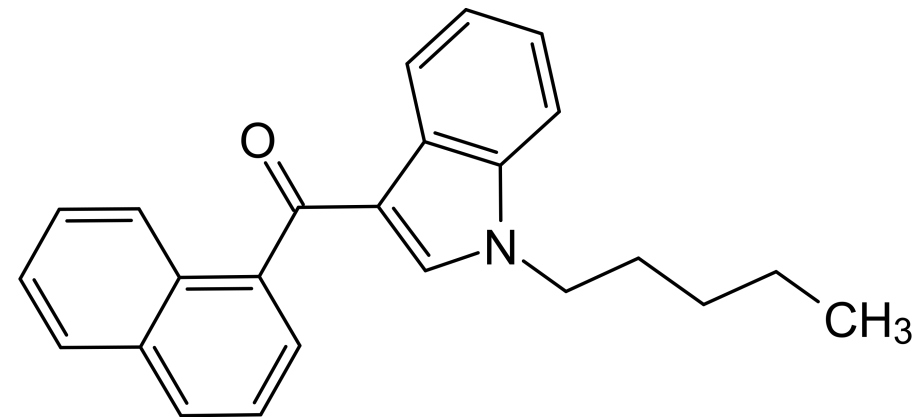
Morpholinoethyl

Are NSAIDs
Cannabinoid
Cousins
???

Synthetic Cannabinoids

John Williams Huffman (JWH-X)

- John William Huffman synthesized numerous cannabinoids
- JWH-018
 - Synthesized in 1984
 - Clemson University
 - 1-pentyl-3-(1-naphthoyl)indole
 - Also referred to as AM-678
 - Naphthoylindole analgesic
 - CB1 and CB2 agonist



Mayo Clinic Proceedings. 2019;94:1840-1851.

Atwood. *Br J Pharmacol.* 2010;160(3):585-593.

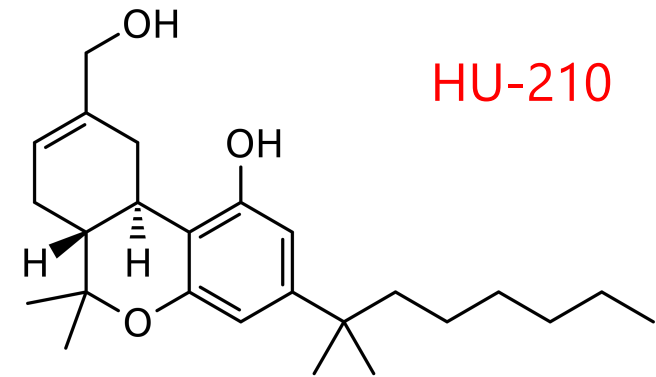
pubchem.ncbi.nlm.nih.gov/compound/1-Pentyl-3-_1-naphthoyl_indole.

Synthetic Cannabinoids

Hebrew University (HU-X)

HU-210

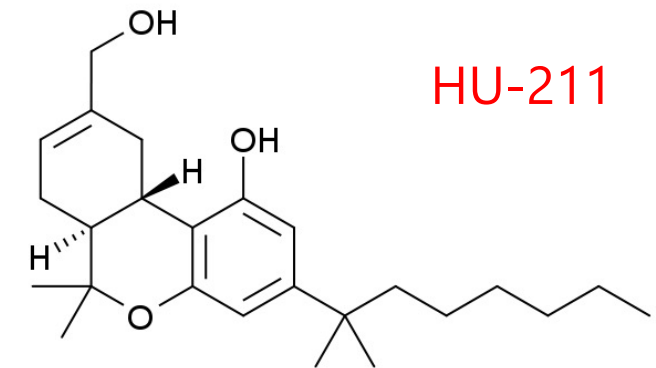
- (-) Enantiomer of 11-OH-D⁸-THC-DMH
- Cannabinoid (CB-1 agonist)
- Potent analgesic



HU-211 (Dexanabinol)

- (+) Enantiomer of 11-OH-D⁸-THC-DMH
- Not an active cannabinoid
- Acts as an NMDA antagonist

➤ Both HU-210 and HU-211 are unique synthetic cannabinoids that are actually very structurally similar to THC



Mayo Clinic Proceedings. 2019;94:1840-1851.

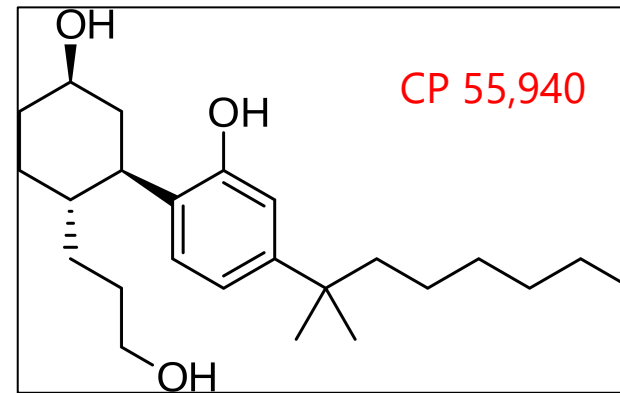
Wilson. Cell Biol Int. 1996;20(2):147-157.

Synthetic Cannabinoids

Charles Pfizer (CP-X)

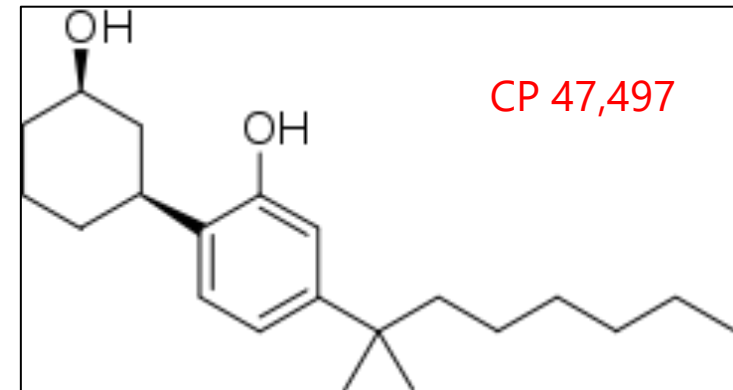
- CP 55,940

- Cyclohexylphenol
- Pfizer developed in 1974



- CP 47,497

- Pfizer developed in 1980's
- Potent CB1 agonist
- "Spice" ingredient



Synthetic Cannabinoids

2nd Generation

Alkyl derivatives

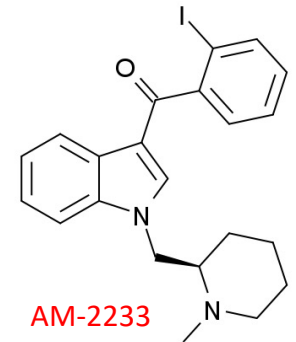
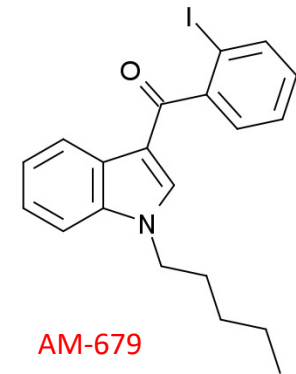
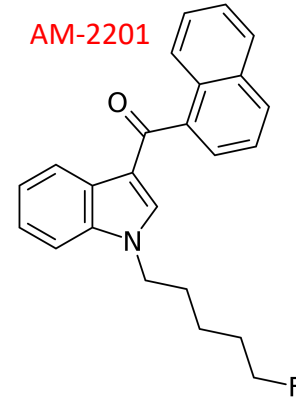
- AM-2201, MAM-2201, and AM-694
 - Alexandros Makriyannis (1st scientist to synthesize)

N-methylpiperidines

- AM-2233 and AM-1220

Benzoindoles

- AM-679 and RCS-4

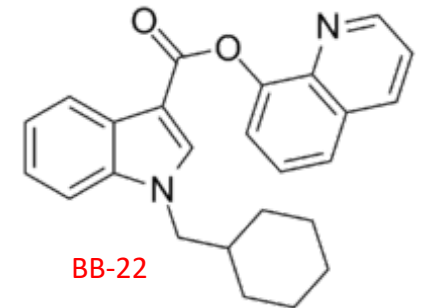
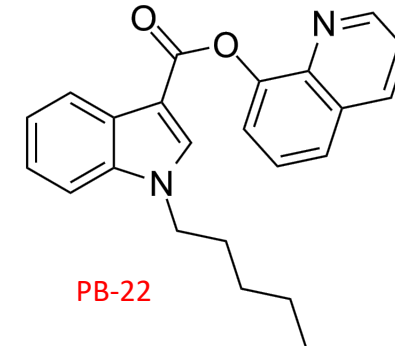
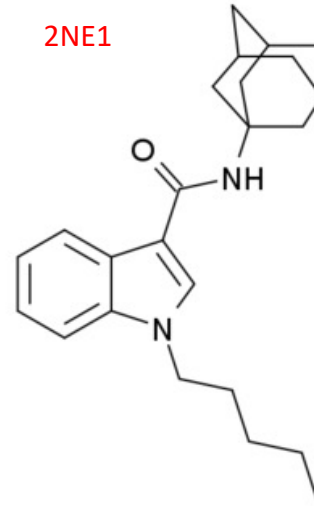


Synthetic Cannabinoids

3rd Generation

Indoles

- 2NE1/APICA/SDB-001
 - 2NE1: North Korean Girl Band
- PB-22 (QUPIC)
- BB-22 (QUCHIC)



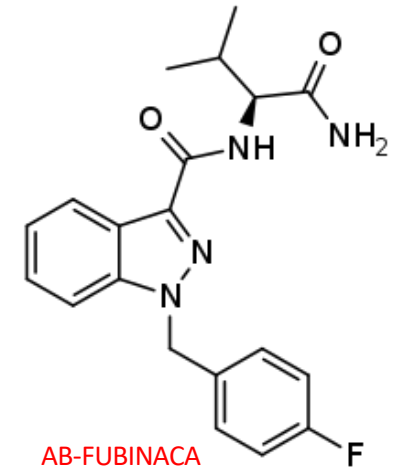
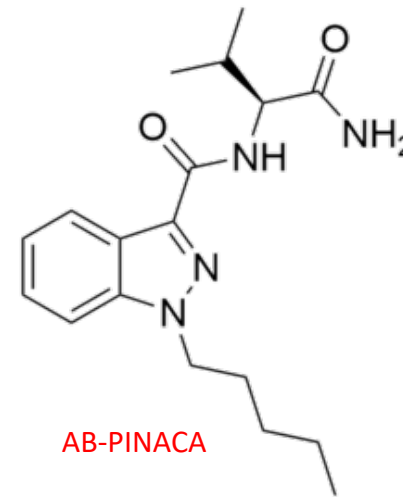
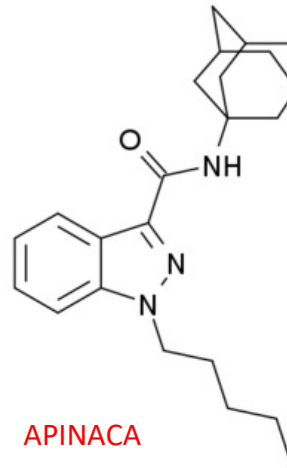
Mayo Clinic Proceedings. 2019;94:1840-1851.
Uchiyama. Forensic Toxicol. 2013;31:223-240.

Synthetic Cannabinoids

3rd Generation

Indazoles

- AKB-48/APINACA
 - AKB48: Japanese Girl Band
- AB-PINACA
- AB-FUBINACA
 - CB1 agonist (Pfizer, 2009)

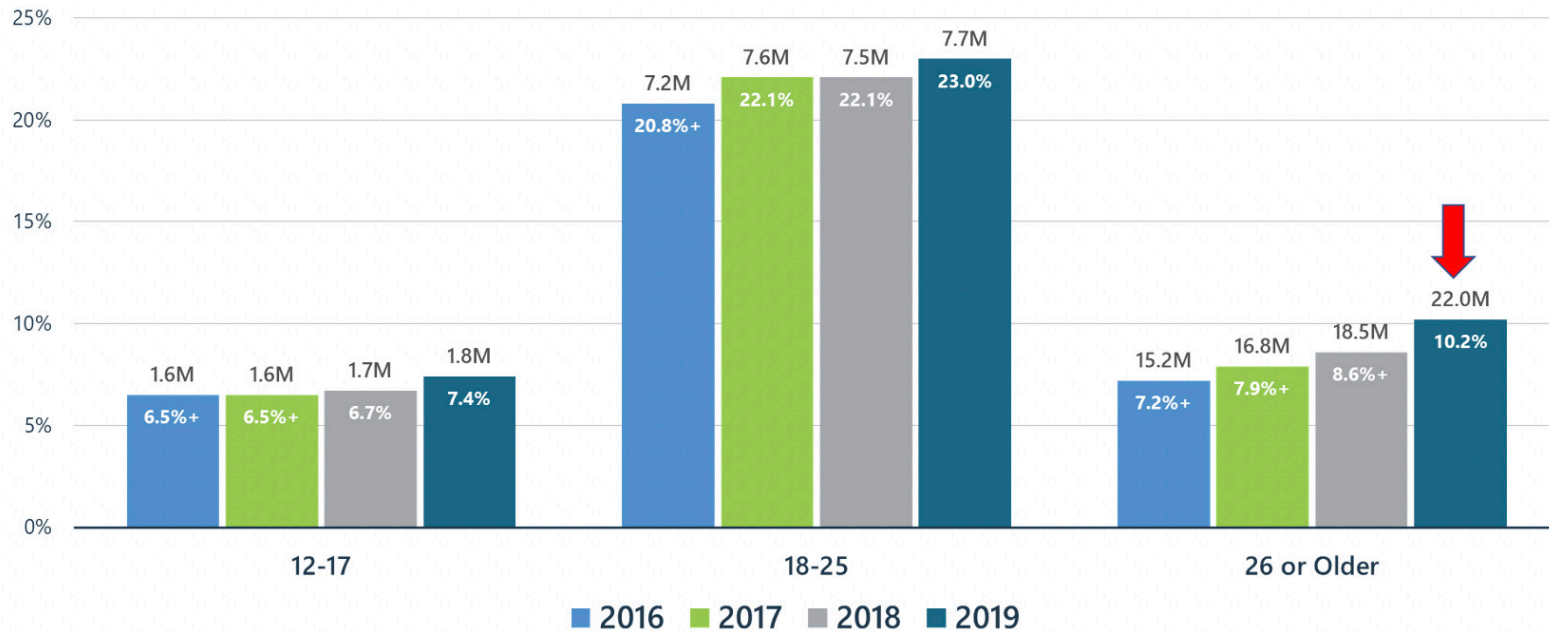


Cannabis Utilization

Marijuana Use

Past Month Marijuana Use for All Age Groups

PAST MONTH, 2016-2019 NSDUH, 12+

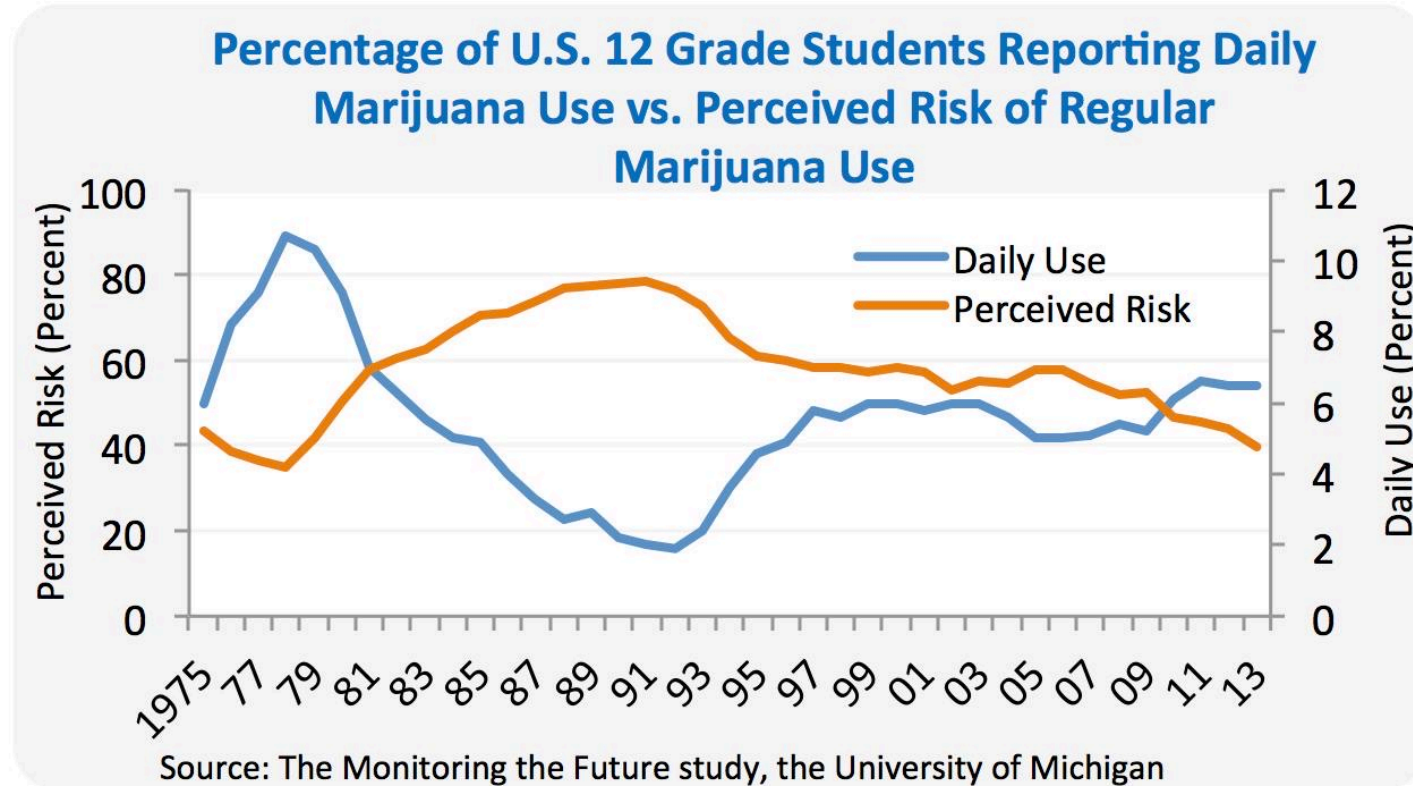


+ Difference between this estimate and the 2019 estimate is statistically significant at the .05 level.



National Survey on Drug Use. SAMHSA. 2019.

Marijuana Utilization vs Perceived Risk

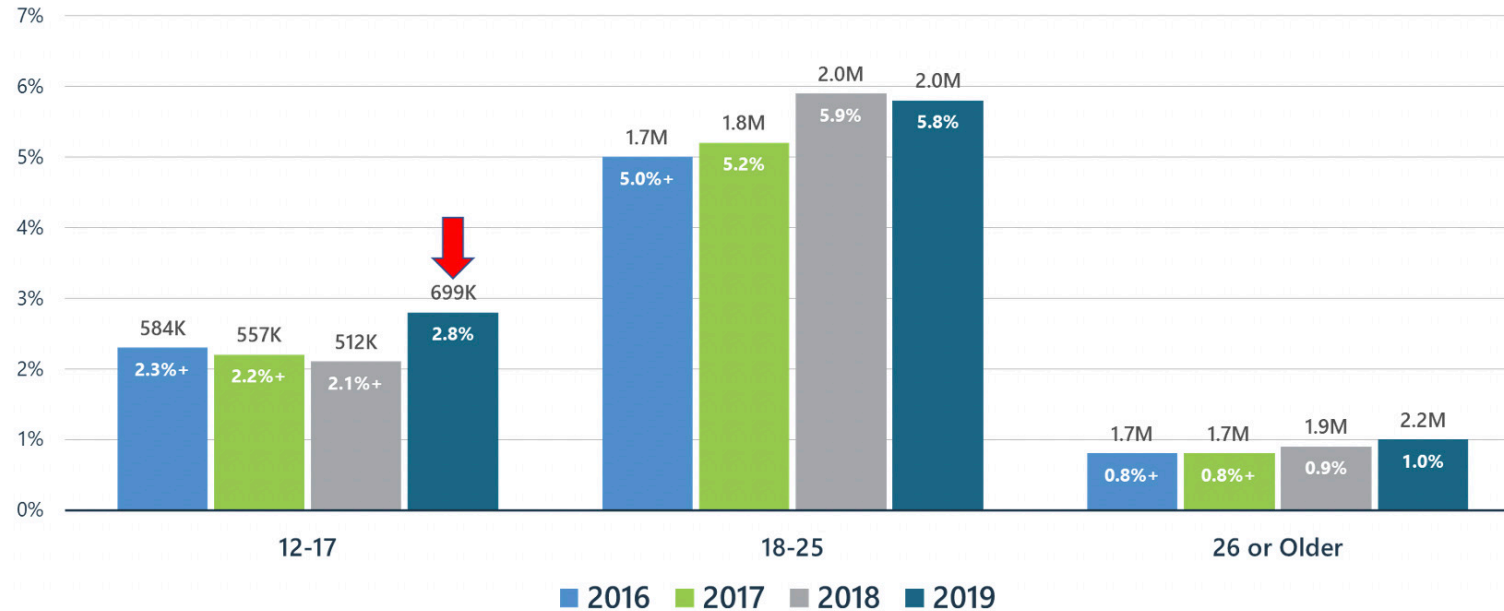


www.drugabuse.gov/news-events/news-releases/2019/12/vaping-of-marijuana-on-the-rise-among-teens.

Marijuana Use Disorder

Marijuana Use Disorder: Significant Increase for 12-17 y.o.

PAST YEAR, 2016-2019 NSDUH, 12+

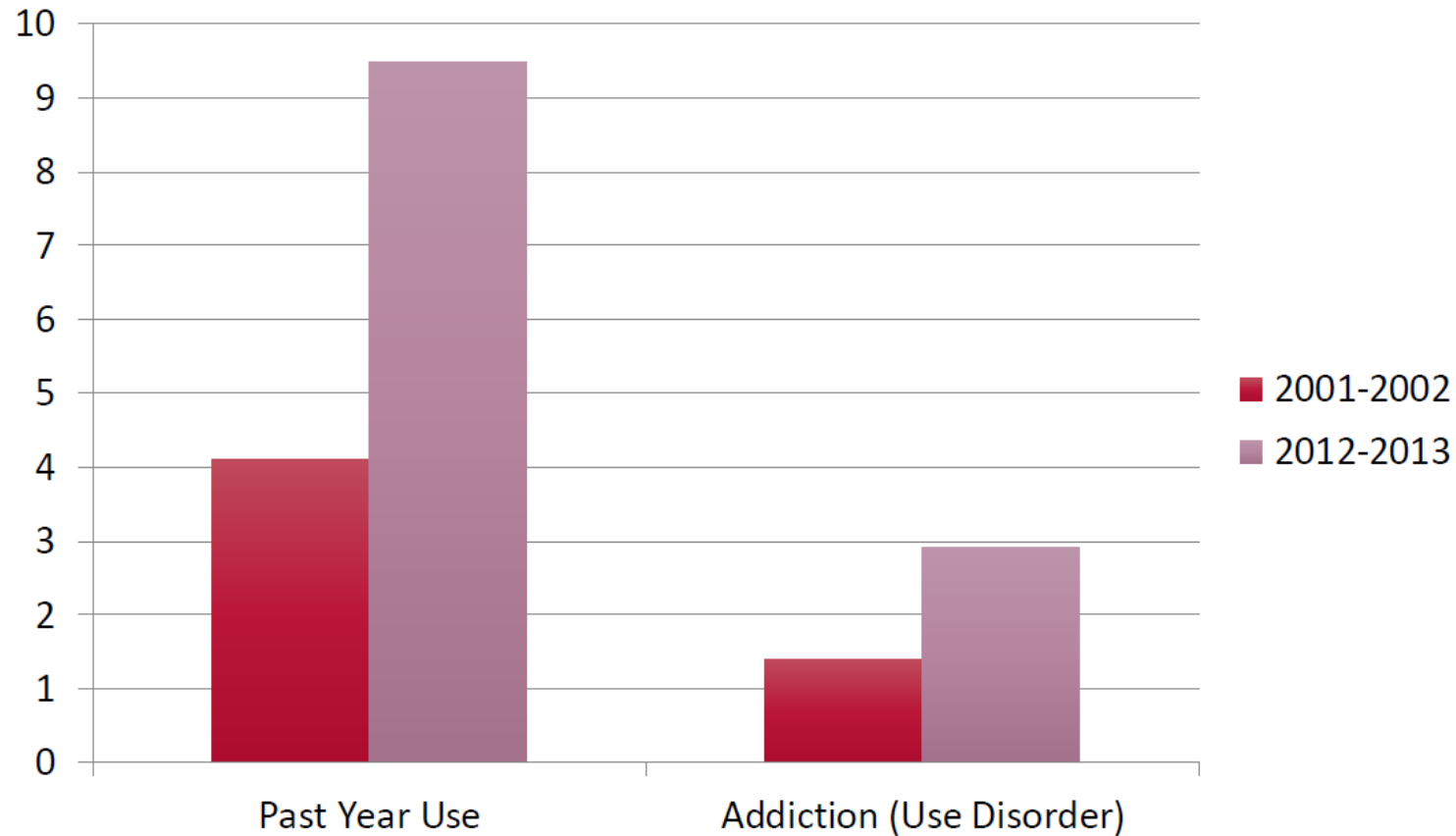


+ Difference between this estimate and the 2019 estimate is statistically significant at the .05 level.

SAMHSA
Substance Abuse and Mental Health
Services Administration

National Survey on Drug Use. SAMHSA 2019.

Marijuana Use and Addiction (2001 to 2013)

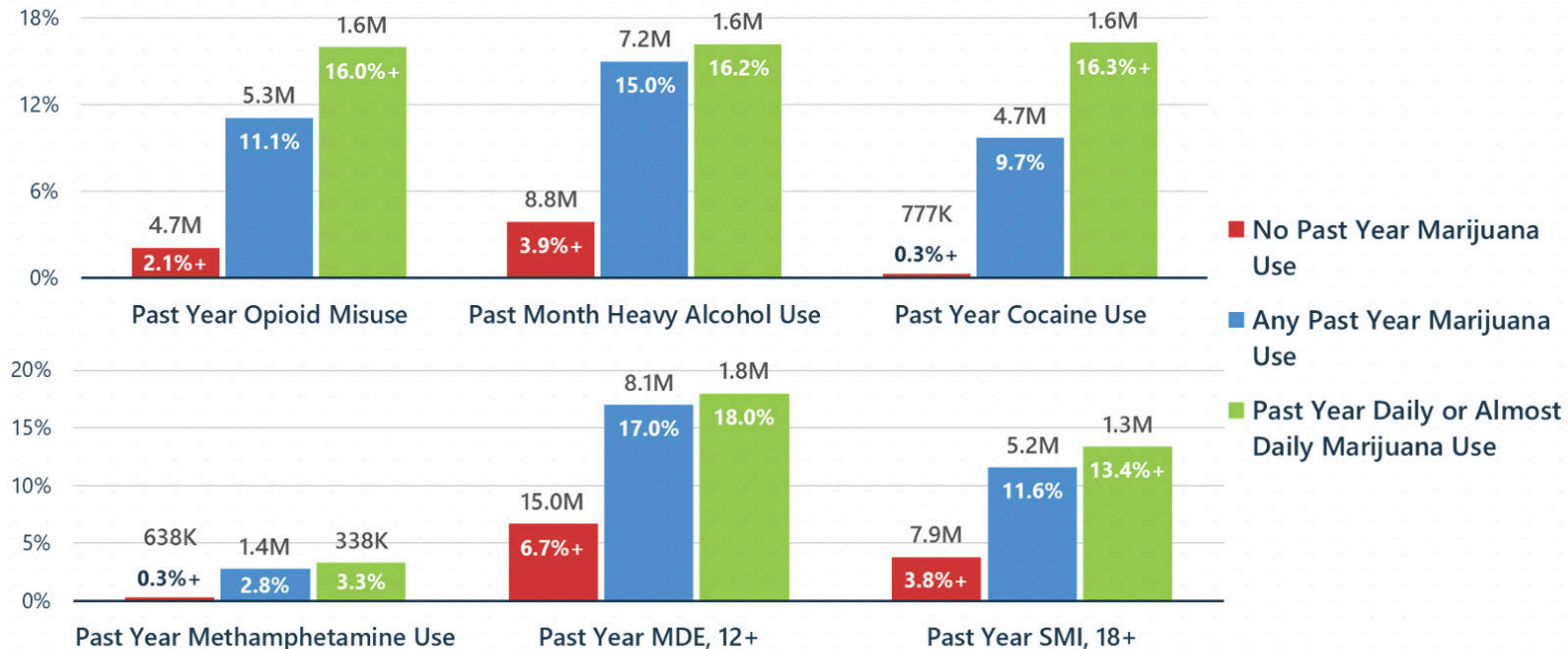


Hasin. *JAMA Psychiatry*. 2015;72(12):1235-1242.

“Street” Polypharmacy

Marijuana Use Related to Other Substance Use, MDE and SMI

PAST YEAR/MONTH, 2019 NSDUH, 12+



+ Difference between this estimate and the estimate for people with past year marijuana use is statistically significant at the .05 level.



National Survey on Drug Use. SAMHSA 2019.

There's No "I" in Pill ???

- Opioid addiction → buprenorphine, methadone, and/or naltrexone (HAT?)
 - Alcohol addiction → naltrexone, disulfiram, or acamprosate (hospital beer?)
 - Cocaine/meth addiction → ? (naltrexone, bupropion, Rx amphetamines?)
 - Cannabis addiction → ? (more cannabis/cannabinoids, nabiximols?)
- All of the above → psychological treatment (teamwork)

National Survey on Drug Use. SAMHSA 2019.

Many Substances, Many Problems, Few Solutions

Is All Substance Use Always a Problem?

The Secret Lives of Functioning Heroin Users

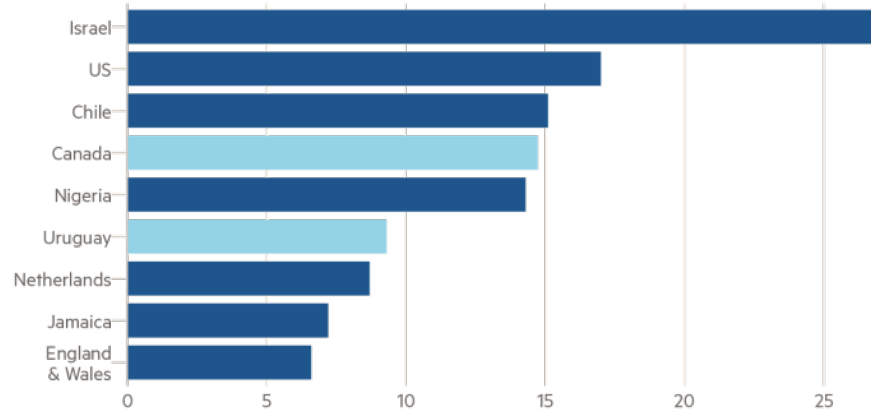
"I use on a lunchtime at work, only a couple of lines or so, which I smoke in the handicap bathroom."

DH By David Hillier **High users**

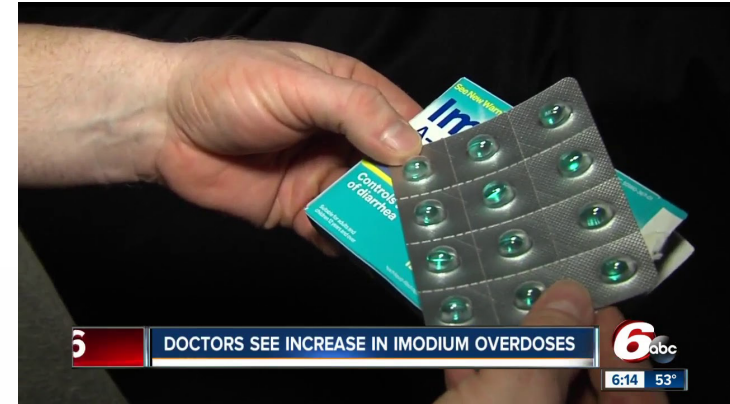
Prevalence of cannabis use in 2017* (% of adult population)

Recreational use legalised

September 15, 2017, 4:45.



*Or latest year; top five and selected countries
Source: United Nations Office on Drugs and Crime
© FT



Yep, that's Bayer's Heroin!

Between 1890 and 1910 heroin was sold as a non-addictive substitute for morphine.

It was also used to treat children suffering with a cough.

www.youtube.com/watch?v=gPzP7_OBR_8

www.ft.com/content/f9d61f58-d78c-11e8-ab8e-6be0dcf18713

www.vice.com/en/article/3kanzw/the-secret-lives-of-functioning-heroin-users

www.verywellmind.com/what-not-to-say-to-someone-who-smokes-marijuana-67777

Painweek.

ADVANCED EDUCATION

CERTIFICATION SERIES

CANNABINOIDS

A repeating pattern of cannabis leaves in a dark green color, serving as a background for the 'CANNABINOIDS' text.

Medical & Recreational Marijuana

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